PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/05 — A1

(11) International Publication Number: **WO 00/16692**

(43) International Publication Date: 30 March 2000 (30.03.00)

(21) International Application Number: PCT/US99/21680

(22) International Filing Date: 17 September 1999 (17.09.99)

(30) Priority Data:
60/100,804 18 September 1998 (18.09.98) US

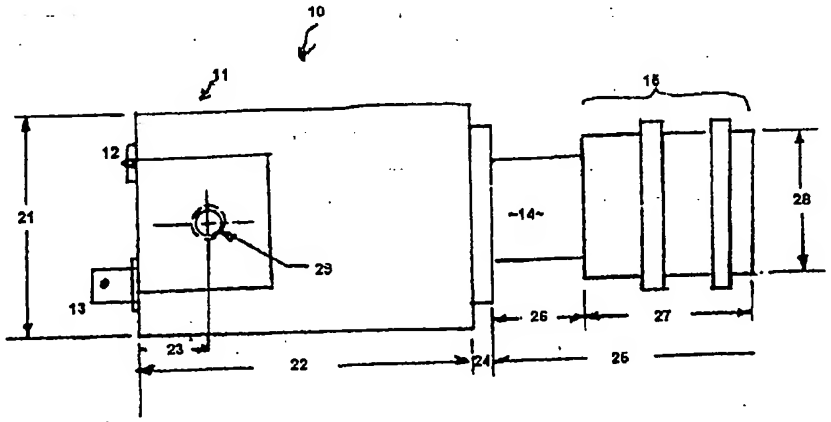
(71)(72) Applicants and Inventors: PRONIEWICZ, Walter, K. [US/US]; 3300 Barhite Street, Pasadena, CA 91107 (US). WINTHER, Dale [US/US]; 4745 Briggs, La Crescenta, CA 91214 (US).

(74) Agent: POPLAWSKI, Edward, G.; Pretty, Schroeder & Poplawski, LLC, 444 South Flower St., 19th Floor, Los Angeles, CA 90071 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NONINVASIVE MEASUREMENT OF BLOOD SUGAR BASED ON OPTOELECTRONIC OBSERVATIONS OF THE EYE



(57) Abstract

Electromagnetic radiation reflectivity from the body is measured. One form of the invention measures essentially without spectral analysis. The eye (30) is an advantageous part of the body for measurement. A monochrome detector array, e.g., black, and white CCD camera (10), suffices for the measurements. The apparatus detects changes in level of the reflected radiation, and relates the changes to glucose concentration. The relationship is monotonic as between glucose, and amount of reflected radiation. The system may operate with visible light, particularly in the yellow/green, or both; and may take into account a reverse signal response in the red IR, or both.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

NONINVASIVE MEASUREMENT OF BLOOD SUGAR BASED ON OPTOELECTRONIC OBSERVATIONS OF THE EYE

RELATED U. S. PATENT DOCUMENTS

This application claims priority of United States Provisional Patent Application serial 60/100,804 of Walter K. Proniewicz and Dale E. Winther, filed on September 18, 1998, and now wholly incorporated by reference into the present document. Except for a prior-patent listing and some commentary about prior art which appear below, this application is based substantially exclusively upon that provisional application and is accordingly believed to contain no new matter with respect to that application.

FIELD OF THE INVENTION

This invention relates generally to noninvasive blood testing; and more particularly to optoelectronic determination of glucose concentration in the blood, also called "blood sugar". Optoelectronic determination of glaucoma overpressure within the eye is also introduced.

BACKGROUND OF THE INVENTION

In various scientific and medical applications, blood testing is an invasive procedure, sometimes requiring blood to be drawn several times a day. This is true in particular for sufferers of diabetes — including one of the present inventors.

Existing methods use hypodermic syringes inserted into veins or arteries, and lancing devices for fingertips and

earlobes. With these methods, frequent blood testing is uncomfortable and even frightening, particularly for young children and the very ill — or those with collapsed veins.

Furthermore people with a chronic condition or illness often experience pain, infection, or loss of feeling due to scarring, as a result of frequent self-testing. These negative considerations discourage many from taking responsibility for their own illnesses, thus deterring them from enjoying a full, normal life.

After blood has been drawn and placed on an indicator strip, it can be analyzed for blood glucose by handheld devices that perform spectral analysis of the blood on the strip. Some of these devices are nominally subject to plus-or-minus twenty- or thirty-percent error, and it is commonplace for two such devices to report blood-sugar values differing by 80 mg/dL and more — even when the reported values are both well below 200 mg/dL.

Some United States patents, adduced by a professional searcher, that may be relevant to the present invention are 5,713,353; 5,572,596; 5,471,542; 5,433,197; 5,432,866; 5,291,560; 5,016,282; 4,641,349; 3,958,560; and 3,533,683.

Thus the blood-monitoring field has failed to provide methods for determining blood glucose and other blood constituents precisely, accurately, and without the pain, infection and other physiological and psychological detriments mentioned above. As can now be seen, prior art in this field is subject to significant problems, and have left room for considerable improvement.

SUMMARY OF THE DISCLOSURE

The present invention introduces such improvement. The invention has several facets or aspects which are usable independently — although for greatest enjoyment of their ben-

efits we prefer to use them together, and although some of them do have some elements in common.

In preferred embodiments of a first of its independent aspects, the invention is noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from the body. The apparatus includes some means for directing electromagnetic radiation to such body. For purposes of breadth and generality in discussion of the invention we shall refer to these means simply as the "directing means".

In addition the apparatus includes some means for receiving and measuring electromagnetic radiation reflected from such body substantially without spectral analysis of the reflected electromagnetic radiation. Again for generality and breadth we shall call these the "receiving and measuring means".

The foregoing may represent a description or definition of the first aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, this facet of the invention entirely eliminates need for piercing the body or otherwise obtaining blood samples, and so avoids the discomfort, fear and other detriments discussed above. Furthermore this aspect of the invention is advantageous in that it requires no elaborate spectral modulation, or multiple detectors for different wavelength regions, or dispersive elements — such as required to perform spectral analysis.

The absence of requirement for spectral analysis is a direct result of our very interesting discovery that electromagnetic radiation reflected from the iris bears a monotonic relationship (though different in different wavelength regions) to glucose concentration in the blood. In consequence, the apparatus is remarkably simple, economical and reliable.

Although the first major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the directing means direct electromagnetic radiation to an eye of the body; and the receiving and measuring means include some means for receiving and measuring electromagnetic radiation reflected from the eye.

Further preferably the receiving and measuring means comprise a monochrome detector array — and in this case still more preferably the monochrome detector array comprises a black-and-white charge-coupled-detector (CCD) camera. Another related preference is that the receiving and measuring means include a digital processor for analyzing signals from the CCD camera.

More generally, such a processor is desirable for analyzing signals representative of quantities of the reflected electromagnetic radiation. In this case one preference is that the digital processor be part of a personal computer, and the blood glucose level is reported on a monitor screen of the computer.

An alternative preference, however, is that the apparatus be a handheld portable unit, that the unit include reporting means for indicating the blood glucose level, and that the digital processor be part of the handheld portable unit. In this case preferably the reporting means include an LCD unit for visually indicating the blood glucose level.

Another basic preference is that the receiving and measuring means include some means for detecting change in level of the reflected electromagnetic radiation, and relating said change to blood-glucose concentration. Still another is that the receiving and measuring means include some means for detecting change in level of the reflected electromagnetic radiation — and also some means for reporting glucose concentration that varies substantially monotonically with reflected-electromagnetic-radiation level. Another general preference is that the detecting means

include some means for responding to reflected visible light — and, in this case, particularly to light in the yellow or yellow-green portion of the spectrum, or both.

Although the apparatus has been described as operating substantially without spectral analysis, this is not intended to imply that the apparatus is necessarily entirely unable to differentiate between spectral regions. For instance, preferably the apparatus includes some means for eliminating response to some particular electromagnetic-radiation band — e. g. the red or infrared, or both. Similarly the means for receiving and measuring substantially without spectral analysis preferably do take into account a reverse signal response in the red or infrared, or both.

Other preferences will appear in regard to this first aspect (and the others as well) of the invention, in the "DETAILED DESCRIPTION" section that follows.

In preferred embodiments of a second major independent facet or aspect, the invention is a noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from the body. The apparatus includes a self-contained case.

It also includes some means, mounted to the case, for directing electromagnetic radiation to the body. Also included are some means, mounted to the case, for receiving and measuring electromagnetic radiation that is reflected from the body.

The foregoing may represent a description or definition of the second aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, because we have established through prototype experimentation and testing that the entire invention is capable of reduction to be carried within a self-contained case, the many benefits of noninvasive measurement can be enjoyed in a unit that need not take the form of a

machine only suited for use in a medical facility. Rather, the invention can be implemented in a machine suited for patients' use at home, or at an ordinary office or other business — or in cars, restaurants, etc.

Although the second major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the case is fully portable. Also in this instance preferably the case fits in the palm of a normal-size adult's hand.

In preferred embodiments of a third of its major independent facets or aspects, the invention is a noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from an eye of the body. The apparatus includes some means for directing electromagnetic radiation to an iris of such eye. It also includes some means for receiving and measuring electromagnetic radiation reflected from such iris. Also included is a programmed digital processor that analyzes the measured reflected radiation and computing blood-sugar concentration therefrom — and in particular uses a reflection of the electromagnetic-radiation source, from the eye, as a peak amplitude point for image alignment.

The foregoing may represent a description or definition of the third aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, the eye is generally available for optoelectronic measurements without the subject's disrobing or any other great inconvenience. Moreover, condition of the blood in the eye is generally particularly rapid in its response to or tracking of the condition of the blood in other critical parts of the body — particularly the brain.

Although the third major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the receiving and measuring means also include some means for receiving and measuring electromagnetic radiation from a pupil of the eye.

This preference facilitates determination of a baseline dark level, or of an illumination level provided by the electromagnetic-radiation directing means, or both.

In preferred embodiments of a fourth of its major independent facets or aspects, the invention is a blood-glucose measuring method. The method includes the step of imaging forward surfaces of a person's eye on an electronic camera. It also includes digitizing resultant image signals from the camera. Further the method includes — to determine blood-glucose level — processing pixel signals representing the iris, separately from pixel signals representing other parts of the eye.

The foregoing may represent a description or definition of the fourth aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, analysis of conditions in the iris is advantageous in that the iris exhibits monotonic relationships (peculiar to different wavelength regions) between reflected electromagnetic-radiation level and glucose concentration — enabling enjoyment of the previously mentioned benefits of measurement without spectral analysis.

Furthermore the separation of iris and pupil signals for processing is amenable to straightforward implementation based upon geometry, leading to easy compensation for varying illumination level and the like as previously mentioned.

Although the fourth major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the method also includes the steps of processing pixel signals representing the pupil to obtain a baseline dark level or an illumination level, or both — and also applying the dark level or illumination level, or both, to refine the pixel signals representing the iris. In this case advantageously the processing step includes applying an average reflected intensity level of the pupil to represent the dark level baseline.

Another general preference is that the iris-pixel signal processing comprises integrating all usable iris-pixel signals to produce a unitary intensity indication. In this case preferably the applying step includes integrating into the indication only intensities that are higher than that of the pupil.

Yet another basic preference is to include the step of substantially removing image scene and illumination variation. Still another preference is to include the step of calibrating readings for an individual patient.

Another general preference is to include masking out the pupil pixels from the iris region. In this case the masking step also preferably includes applying a software pupil mask that substantially stabilizes the number of iris pixels available for use, and substantially stabilizes pupil centering within the iris image. Further if this is done preferably also the pupil mask is larger than the largest pupil diameter occurring in measurement conditions.

Other general preferences relative to the method of our invention include these steps, considered individually:

- masking out the pupil pixels from the iris region;

- diffusing source electromagnetic radiation to minimize hot spots;

- removing peak signal amplitudes, to minimize the effect of illumination hot spots;

- mapping illumination hot spots, to enable disregarding hot-spot regions in said processing step;

- adjusting image contrast to substantially fill the complete dynamic range of pixel data words;

- looking up the measured level in a lookup table to obtain a corresponding numerical blood-glucose concentration indication in quantity of glucose per unit blood volume; and

- said digitizing step comprises distinguishing electromagnetic-radiation-intensity changes at least as small as one part in ten thousand.

Another preference, still as to the fourth (method) aspect of our invention, is this sequence of steps:

- finding a centroid of the pupil of the eye;
  calculating average brightness around a pupil centroid;
- masking out the pupil region of the eye;
- equalizing the iris image using the pupil brightness as a level baseline;
- removing hot spots if present;
- integrating all of the processed iris pixels to obtain a numerical representation of brightness level of the iris;
- searching a lookup table to apply a previously developed calibration and thereby determine an imputed glucose concentration in quantity of glucose per unit volume; and
- displaying the imputed glucose concentration.

In preferred embodiments of a fifth major independent facet or aspect, the invention is a blood-glucose measuring method for use with a small electromagnetic-radiation source. This method includes the step of automatically finding a reflection, from a patient's pupil, of the electromagnetic radiation.

The method also includes the step of automatically performing a position alignment based upon the location of the reflection of the electromagnetic radiation. The foregoing may represent a description or definition of the fifth aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, this mode of operation very easily resolves several otherwise knotty problems of alignment, which can otherwise threaten the integrity of the overall measurement process — since the process is sensitive to alignment and control of signal returns from the white of the eye as well as the pupil.

Although the fifth major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the method also includes zeroing-out the area within the electromagnetic-radiation source, to form an image of forward surfaces of the eye without the electromagnetic-radiation source.

Another preference, especially when the method is for use with a centrally disposed electromagnetic-radiation source, is the step of growing a pupil mask — starting from the electromagnetic-radiation source as a centerpoint — to cover the pupil area in the image. In this case, preferably the method also includes capturing brightness level in an area under the aligned pupil mask, for use in a dark-level calibration.

In preferred embodiments of a sixth major independent facet or aspect, the invention is apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from an eye of the body. This apparatus includes a detector array.

It also includes a small electromagnetic-radiation source held directly in front of the detector array, for directing electromagnetic radiation to the eye. In addition the apparatus has some means for receiving and measuring electromagnetic radiation reflected from the eye.

The foregoing may represent a description or definition of the sixth aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, use of a source in the described position greatly simplifies, in several ways, the processing of data derived from the optical system. Some specific benefits will be seen in the preferred implementations discussed immediately below and in the later "DETAILED DESCRIPTION" section of this document.

Although the sixth major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the apparatus also includes a lens between the detector array and the electromagnetic-radiation source.

In this case, it is preferred that the electromagnetic-radiation source shine toward the eye from substantially the geometric center of the lens — or, alternatively of the detector array.. In this case the apparatus further includes some means for using a reflection of the electromagnetic-radiation source, from the eye, as a peak amplitude point for finding the image center.

A more general preference, still as to this sixth main aspect of the invention — and especially when the apparatus

is for use in measuring blood-glucose concentration for the body of a human being — is that the electromagnetic-radiation source serve as a visual centering target for the human being. In such a system, the human being looks substantially directly toward the electromagnetic-radiation source to, in substance, automatically align or center (at least approximately) the pupil in the optical field.

In preferred embodiments of a seventh major independent facet or aspect, the invention is apparatus for measuring blood-sugar concentration in a living body, by measuring electromagnetic-radiation reflectivity from blood of the body. The apparatus includes some means for directing electromagnetic radiation to the blood.

It also includes some means for receiving and measuring electromagnetic radiation reflected from the blood substantially without spectral analysis of the reflected electromagnetic radiation. From all the discussion, in this document, of aspects of the invention, those skilled in the field of noninvasive medical instrumentation will understand that the invention operates, in one way or another, based upon presence of the blood in the iris or elsewhere within the body — thereby making the blood available for optoelectronic measurement. Accordingly the invention is not limited to the implementations expressly set forth.

All the foregoing operational principles and advantages of the present invention will be more fully appreciated upon consideration of the following detailed description, with reference to the appended drawings (not to scale), of which:

///

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a somewhat schematic diagram, in plan, of an experimental prototype CCD camera assembly used in preferred embodiments of the invention, and contemplated for adaptation into a commercial unit;

Fig. 2 is a block diagram showing the image input data stream derived from optoelectronic measurements of an eye, using the Fig. 1 camera assembly in a central-illumination arrangement;

Fig. 3 is an isometric view of a representative earlier prototype illumination geometry — one of several attempted, illustrating a diffuse-illumination approach;

Fig. 4 is a like view of a prototype optical bench, particularly including a foam ocular and a forehead rest;

Fig. 5 is a like but more detailed view of the Fig. 4 rest;

Fig. 6 is a like view of an early prototype eye-tracking system;

Fig. 7 is a like view of an early prototype bezel for mounting at the front of the camera lens and for aiming a small electromagnetic-radiation source toward the eye;

Fig. 8 is an enlarged view of the Fig. 7 bezel, shown with electromagnetic-radiation source and eye, in longitudinal elevation generally along the system centerline;

Fig. 9 is an image of part of a representative operator control panel, seen on a computer screen of our prototype apparatus while the system is imaging a subject eye;

Fig. 10 is a like image of another part of the same control panel display, particularly showing histograms representing results of different processing stages within the program;

Figs. 11 through 19 are a G program listing (graphical programming, as explained below) of the digital-processor code that produces output values in "arbits" (arbitrary units) related to glucose concentration;

Fig. 22 is an image like Figs. 9 and 10, but for another display of a control panel — for a second program,

used to correlate arbit values with an actual amount of patient blood sugar in conventional units;

Figs. 21 and 22 represent two pages of G code that represent the entire second program used to obtain calibrated IDN-to-glucose data as just mentioned; and

Fig. 23 is a diagrammatic showing of focal-distance measurements that can be used to determine glaucoma pressure automatically with apparatus analogous to certain forms of the glucose-concentration measuring systems described herein. View A represents a normal-pressure condition, and view B an abnormal or overpressure condition.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

1. OVERVIEW

A method has been found to determine the amount of blood sugar without the need for invasive procedures. This technique can determine sugar levels by analyzing reflected electromagnetic-radiation information from the eye.

The process uses a black & white CCD TV camera and a personal computer. A fully portable version that fits in the palm of one's hand is presently possible.

The combined result of the camera/computer arrangement is a numeric output that displays blood-glucose levels in units of milligrams/deciliter, on a computer screen or small LCD display. A handheld illumination and imaging system is used to take blood sugar measurements.

The system operates by integrating the reflected electromagnetic radiation from the iris portion of the eye — not from the retina. Numerous anterior blood vessels present a means of directly observing bloodstream content with exterior optical methods.

Glucose accumulations in this area produce a change in the intensity of reflected electromagnetic radiation. The

more sugar present, the higher the level of reflected electromagnetic radiation.

This change in electromagnetic-radiation reflection is too small to be seen with normal observation methods. The ability to measure electromagnetic-radiation intensity changes as small as 1 part in 10,000 is required to detect blood sugar changes.

The CCD camera images the eyeball and the image is digitized. These data are processed to remove the pupil pixels. Only the iris pixels are used as representative of glucose values as such, but as explained elsewhere the pupil pixels are used to develop baseline and illumination levels.

The iris pixels are integrated (summed) to produce a single intensity number. We sometimes call this the "integrated data number" or IDN for short; it is interchangeably designated "GLU", for glucose value.

The IDN (or GLU) value can be calibrated by removing image scene and illumination discrepancies. It can be further calibrated to an individual patient to produce an extremely accurate IDN-to-blood-sugar correlation. Repeatable scene geometry is also very desirable for accurate measurements.

2. MASKING AND NORMALIZATION

As mentioned above, the primary IDN calibration technique uses pupil reflection and geometry data. Changes in input electromagnetic-radiation levels are detected by sensing pupil brightness.

The average reflected intensity level of the pupil is used as the dark-level baseline for IDN processing. Only intensities that are higher than that of the pupil are integrated into the IDN.

This is a scene-to-scene automatic electromagnetic-radiation level calibration. If the scene electromagnetic-radiation level goes up, so do the levels of the pupil and the iris.

The pupil level offsets the higher iris level and preserves the scene-to-scene relative brightness. This guarantees that only sugar-level increases will cause measured intensity increases.

A further problem involves changes in pupil diameter and pupil centering within the scene. If these components are not held constant, the total number of iris pixels available for integration will change.

To control these effects, a software pupil mask is employed. This zeroes-out a fixed region around the pupil.

It is larger than the largest pupil diameter and covers pupil-centering errors.

Some iris pixels are zeroed in the process, but all image frames are treated in the same way. The pupil mask is always the same size, and therefore all image frames contain the same number of iris pixels. The geometric distortions due to pupil variations are eliminated.

Another source of error is produced from illumination hot spots. Good electromagnetic-radiation source diffusion is needed to prevent the problem.

Hot-spot removal can be partially accommodated with software. Peak signal amplitudes are removed before the integration process. In addition, Hot Spot mapping can be used to extract the troublesome regions prior to integration.

Image contrast equalization (stretch) is also applied. This causes pixels to fill the complete dynamic range of pixel data words.

The pupil baseline data is applied to this process, permitting only the pixels that are brighter than the pupil to be remapped. As a result, further processing takes place using data that have been scene-level-biased and equalized to a full amplitude range.

3. CALIBRATION AND READOUT

The process of converting the IDN to a true glucose measurement requires a simple lookup operation to verify that the result is within a predetermined error band. The correlation from IDN to milligrams per deciliter (mg/dL) can be seen in the following formula.

$$IGN = \frac{IDN_{max} - IDN_{min}}{GL_{max} - GL_{min}} \cdot GL + IDN_{min}.$$

These terms are defined as follows.

IGN = implied glucose number

IDN_{max} = highest possible IDN (integrated data number)

IDN_{min} = lowest possible IDN

GL_{max} = highest possible glucose value (in mg/dL)

GL_{min} = lowest possible glucose value (mg/dL)

GL = actual glucose value (mg/dL)

Inserting a milligram/deciliter value in GL yields its equivalent IDN value in IGN.

Going from IDN to GL is accomplished by searching or hashing a lookup table. When the IDN value is equal or almost equal to a bounded IDN table value, GL is retrieved from the table and output as the glucose reading.

The IDN lookup table is produced by averaging multiple calibrated IDN samples for known glucose values. A fixed error range is based on a plus-or-minus deviation percentage from the average IDN.

This is done for all available glucose numbers. Because it is difficult to obtain values for every glucose number, values between known samples can be interpolated to create a complete table.

4. PROCESSING STEPS

These are the discrete processes performed by our prototype systems:

- image the eyeball
- find the centroid of the pupil
- calculate the average brightness around the pupil centroid
- mask out the pupil region of the eye
- equalize the iris image using the pupil brightness as a level baseline
- remove hot spots if present
- integrate all of the processed iris pixels
- search a lookup table to find the closest IDN-to-GL match
- display the imputed glucose number in GL

5. IMAGE INPUT PROCESSING

To reduce the complexity of the image-input system, software has been developed to optimize camera positioning and illumination consistencies. We have constructed an apparatus that holds a electromagnetic-radiation source directly in front of the camera lens..

The electromagnetic radiation is made to shine onto the eye from the geometric center of the lens. This results in even illumination of the eye, eliminating reflections and hot spots.

Two additional effects are created by this central-illumination geometry:

- the electromagnetic-radiation source becomes a visual centering target for the patient; and
- the electromagnetic-radiation source becomes a peak amplitude point for finding the image center.

The software finds the electromagnetic radiation (seen as a hot spot in the center of the pupil) and performs a position alignment based on its location.

Having found the center of the pupil, the software also performs the following processes.

- zero-out the area within the electromagnetic-radiation source, to eliminate the electromagnetic-radiation source from the pupil image
- determine the eye registration within the camera frame, and calculate the useful image area
- grow a pupil mask from the electromagnetic-radiation-source centerpoint and use it to cover the pupil area in the image
- capture the area under the aligned pupil mask for the dark-level calibration

Additional system sensitivity and accuracy can be obtained by capturing multiple frames and summing their IDNs together. Changes due to small movements of the eye are thereby averaged out. Digitally summed IDNs also increase effective integration time, resulting in a larger dynamic range.

6. WAVELENGTH EFFECTS

It has been observed that most visible light colors work well for glucose detection. Peak response appears to be in the yellow and yellow/green portion of the spectrum for the algorithm described above.

A reverse signal response takes place with near infrared illumination. The higher the glucose level, the lower the reflected electromagnetic-radiation.

This reverse effect can also be seen in the red region of the visible spectrum and can disturb the linearity of the glucose response. If the visible portion of the spectrum is used for the measurement, then using LED light sources that contain little or no red or infrared components improves measurement accuracy.

It is reasonable to generalize the foregoing observations, however, though this is not mentioned explicitly in our provisional application, to note what is common to both wavelength regions — i. e. that the level response is substantially monotonic, namely either an increasing function or a decreasing function for the different wavelength regions respectively.

The infrared reverse effect can be used to improve system accuracy. Infrared illumination yields a nonlinear conversion that produces a large dynamic range in the low-sugar region. This information can be processed for enhanced low-end performance.

A combination of visible and infrared processing can be done to produce dual response tables. These "inverse" response tables can be correlated to automatically verify the validity of glucose measurements. This technique produces additional accuracy and means of system self-calibration.

Our provisional application introduces the embodiments disclosed above, in which a black-and-white CCD array is able to collect sufficient information for blood-glucose determination — reflected electromagnetic-radiation level being distinctly correlated with glucose concentration.

This is accomplished through heavy reliance upon further electronic manipulation of the data. Such operation is mechanically and optically simpler than, and is to be distinguished from, the measurement mode that is also reported in our provisional application — and embodied in earlier prototypes of our apparatus — which employed rotating filter wheels to perform rudimentary spectral differentiation.

7. FURTHER HARDWARE DETAILS

A high-resolution black-and-white digital video camera assembly (Fig. 1) uses a charge-coupled detector (CCD) array as a sensor. The camera includes a body 10 for housing the CCD array, a mounting section 11 with an attachment thread 29, a camera bias-voltage connector 12, and a video-out connector 13.

It will be understood that all of the details presented here relate to experimental prototypes that we have built and tested. Representative dimensions for the assembly follow.

marked dimension	value (inches)	
21	2.18	
22	3.75	
23	0.75	
24	0.69	(CCD setback)
25	2.38	
26	0.75	
27	1.25	
28	1.40	

An extension tube 14 holds a 1:1.4 lens 15, making the focal length approximately 2½ cm (one inch). The purpose of the extension tube is to maximize the amount of data from

the iris 32 (Fig. 2) of the eye 30 and limit, to zero, the amount of white of the eye.

At the beginning of testing, "Snappy™" shots were selected. A Snappy, manufactured by Play Inc., is an image-capture card for a personal computer (PC). It captures a one-thirtieth-second frame from a moving image and stores it for future analysis.

Approximately forty percent of all frames were lost because of movement of the eye, reflections, and exposed white of the eye. The frames used are advantageously similar; the total digital numbers are preferably as close to each other as possible.

To produce optical data for the camera, a small electromagnetic-radiation source 33 (Fig. 2) directs electromagnetic radiation 34 toward the center of an eye 30, and reflections 35 from the pupil 31 and iris 32 traverse the lens 15 to the CCD camera 10. Note that no optical dispersing or wavelength-selecting device is included.

Thus the CCD camera 10 sees the reflected electromagnetic radiation 35 from the eye. Raw video data 37 go to a digital interface 38, which responds with corresponding digital data 39 that proceed into a computer 40.

The central-illumination arrangement of Figs. 1 and 2 was the successor to numerous earlier efforts based instead on diffuse illumination of and data collection from the eye. In the first successful, repeatable one of those (Fig. 3), electromagnetic radiation from a forty-watt incandescent party bulb 43 was integrated by flat white paint on the walls of the room itself — essentially a large integrating-sphere concept.

The electromagnetic-radiation was arranged to approach the eye 30 at a right angle to the optical axis 41 between the lens and the eye, to minimize formation of reflections and shadows. To minimize the problem of hot spots and resulting high data counts, mostly caused by bare exposed lightbulbs, the illumination was passed through a diffuser 42 — created from a plain white paper cylinder placed around the electromagnetic-radiation source.

To lessen the difficulties of repeating frames and holding the CCD camera steady, and to shield and eliminate reflections, an optical bench with a foam ocular 45 (Fig. 4) was built. In addition, a headrest (Fig. 5) helps stabilize the eye.

The optical bench, three feet long, was fashioned from two aluminum rails 47 (Fig. 4) — a rectangular one, lying horizontal, and a square bar turned on the diagonal so that one corner fits into corresponding notched grooves in the base 48 of the headrest and in the base of the camera support. The bar allows movement only along the z-axis (i. e., longitudinally). This geometry also allows setting of distances between the headrest (i. e., the eye position) and the camera.

The support stand allows up-and-down (y-axis) adjustment by means of a vertical rod with an adjustment knob. The two rails are kept parallel by being mounted on two eight-inch crossbars with three legs made from machinist jackscrews. One leg is attached to the center of the crossbar; the other two legs are attached at opposite ends of the other crossbar, thereby allowing leveling in a classical manner.

The headrest is mounted to a sliding aluminum base 48, to support two one-foot-long threaded vertical rods 54 holding a curved aluminum forehead piece 46. The whole mechanism is mounted on a centered vertical support rod 53. A crossbar 52 supports a subject's chin on a soft pad (not shown), and the forehead rests against the forehead piece 46 to stabilize the head. Adjustment and locking are facilitated by an adjustment screw 52.

The CCD camera is also mounted on a support rod, set in a commercial support stand. The rod is attached to the camera, which is inside a tubular cardboard electromagnetic-radiation shield 49 (made from a cardboard mailing tube). A trapdoor allows for adjustments to the camera with two camera-support screws through the tubular shield, centering the camera in the shield.

The tube is four inches in diameter and fourteen inches long. The trapdoor is eight inches long and sections out half of the tube, starting one inch back from the front. The camera lens face is flush with the end of the tube. The interior of the tube is painted flat white.

Various other experimental setups included some geometries with two tubes — one for each eye, with an eye-tracker disc placed in front of the eye not being sampled. We have settled, however, on a system with no ocular lens and in which the nondata eye is exposed for reasons that will become apparent.

In one experimental setup, a pair of slip-tube swing arms 69 (Fig. 6) fixed to the camera mounts — above and below the tubular shield 49 — held a vertical rod 61 on which a block 62 slides up and down 64, carrying a electromagnetic-radiation-emitting diode (LED) 63. The LED served as the electromagnetic-radiation source for central illumination. The slip tubes enabled horizontal adjustments 66, and the LED block vertical movement 64.

The next development in our experimental progression eliminated use of a mechanical eye-tracker. A video monitor is used to show real-time video of the eye being viewed for data collection.

The subject views his or her own eye on the monitor, and can rapidly correct for positioning of the eye, thus minimizing the amount of white of the eye showing — and allowing for detection of unwanted reflections. Looking at a real-time video is faster and easier than doing eye-tracking using the mechanical tracking system.

Selected single frames were stored using a frame grabber or Snappy™ image-capture card. In this process, data collection took a long time because frames with high data error — usually half of the frames taken — had to be discarded.

Next a video recorder was employed. For experimental purposes the start time, lamp color, filters, blood sugar values, commentary and end time were annotated audibly.

Four to five minutes of video data were taken continuously. The end result was thousands of frames (at a frame rate of thirty per second) from which to handpick later.

Good frames could be selected, saving a great amount of time. This also proved that the accuracy and repeatability were very high, much better than current blood-glucose meters on the market at twenty- to thirty-percent error.

Experimental work also explored numerous illumination arrangements with multiple electromagnetic-radiation sources, including arrayed LEDs of different colors in various geometries. Currently favored illumination geometry, however, as noted earlier provides a single electromagnetic-radiation source such as an LED 33 (Fig. 8).

In the best of these configurations, the LED was held centered by a diametral vane or web 72 (Figs. 7 and 8) with a hollow central hub 73 for the LED, in an aluminum bezel 71. The LED is held in front of the camera lens and aimed at the eye.

The back of the LED is covered with black tape 81 to shield the lens (surface) 15 so that none of the direct LED electromagnetic radiation is picked up by the camera. Only the electromagnetic radiation reflected by the pupil 31 and iris 32 is seen by the camera. This scheme also enables the subject to center the subject's own eye by looking directly into the LED — or a grain-of-wheat size incandescent bulb.

Bezels were made to accommodate two sizes of LED: a so-called "T1" 3mm and a "T-1¾" (5 mm). The larger LED masks the entire pupil — thereby negating the data that would be gathered for pupil calibration. The data collected is nevertheless very useful in obtaining the correction factor to establish total system linearity.

The bezel portion that goes over the lens shade has a 1.39 inch inside diameter, with a 0.05 inch wall, 0.3 inch deep. The web that holds the LED has a thickness of 0.04 inch (to minimize the masking of data from the iris to the CCD camera) and is 0.125 inch deep.

A goal during data-taking is to illuminate the iris to the point, at least, 1/2 full well on the total digital number (D/N) possible — or alternatively full well of the CCD camera. Empirical data-collection and -manipulation suggests that 1/4 full well may be a minimum needed to provide the amount of data necessary for all manipulation of calibration, subtraction and averaging for our experimental prototype system.

Whereas our experimental efforts have employed a PC for data manipulation to get a glucose value, our invention contemplates — as a first step toward portability — making a hybrid integrated circuit to replace the PC. It also appears worthwhile to develop a "foolproof" transmitter coded to transmit blood-sugar values directly to a diabetic's insulin pump, as well as calculation of utilization time and amount of insulin. Eventually continuous readings through a convenient means — such as for example eyeglass-mounted sensors — would bring the diabetic and others back to a more-normal life.

8. IMAGE-PROCESSING SOFTWARE

Two programs, "Glucon™" and "Average", were written for implementation of the present invention and were instrumental in performing research and obtaining quantitative results from our experimentation. Both programs were developed from scratch using a graphical programming language known as "G™", and also known as LabView™ 5.0 — with the IMAQ™ imaging tools.

A so-called "graphical programming language" accepts program commands, including flow of logic, not as verbal syntax but rather in the form of geometrical connections and relationships among diagrammatic elements as in Figs. 11 through 19. Such graphical entries, however, are interpreted by a compiler analogously to the way in which verbal

syntax is interpreted in use of more-traditional programming languages.

Glucon has several experimental features (filters, pixel comparison algorithms, adjustable display mode, etc.). It evolved during early experimentation phases to permit trial-and-error analysis of the image data. In the state described here, it is used to process eye image input and automatically yield the final glucose measurement as described above.

While our system is imaging a subject eye, them computer screen displays an operator control panel (Fig. 9) that includes various buttons and other controls — and also both the image presentation (at left) and the GLU or IDN values in milligrams per deciliter (mg/dL) as calculated from the images. In addition, histograms show (Fig. 10) the results of different processing stages within the program.

The G program produces the results described above. The first program, Glucon (listed in Figs. 11 through 19), is the software key to extracting information in accordance with this invention. It embodies all necessary algorithms and techniques for primary operation of the invention to obtain IDN or GLU values.

The second program, Average, is used to correlate the IDN or GLU values obtained from an imaged eye with the actual amount of patient blood sugar. It processes a user-selectable number of images of a subject eye, all taken at a particular sugar level — i. e. in quick succession.

In operation, Average creates a statistical box and then obtains the average and absolute IDN or GLU limits. These values are used to build a table of IDN-to-blood-sugar conversions.

Fig. 20 shows the on-screen operator control panel of Average. Figs. 21 and 22 represent three pages of G code that represent the entire program, Average, used to obtain calibrated IDN-to-glucose data from the IDN or GLU values.

9. GLAUCOMA MEASUREMENTS

Our work has also suggested that curvature of the iris reveals glaucoma pressure at close focal length. An eye machine can be used to automatically give difference in comparative focal lengths of inner iris vs. outer iris as an indicator of pressure.

Here the distance $F_{iris\ ID}$ (Fig. 23) represents the distance from the vertex plane of a CCD camera lens 15 to the inside diameter (ID) of the iris — in other words, to the circular transition between the iris 32 and the pupil 31. Analogously $F_{iris\ OD}$ represents the distance from the lens vertex plane to the outside diameter (OD) of the iris — i. e., to the circular transition between the iris 32 and the white 30' of the eye 30.

In the upper "A" view, these two distances $F_{iris\ ID}$ and $F_{iris\ OD}$ are substantially equal, $F_{iris\ ID} = F_{iris\ OD}$. This indicates a balanced or normal pressure condition within the eye. In the lower "B" view, the two distances are no longer equal: specifically, the ID distance now exceeds the OD distance, $F_{iris\ ID} > F_{iris\ OD}$, thereby indicating abnormal, excessive pressure.

The incremental distance 91, which is to say the difference $F_{iris\ ID} - F_{iris\ OD}$ (or ratio) between the two distances, is related to pressure. Focal determinations thus yield a measure of intraocular pressure, a large distance corresponding to high pressure and a small distance to low pressure. Depth of field, for example 0.3 mm (0.012 inch), may form a limitation on this technique.

It will be understood that the foregoing disclosure, and that of the following Appendix, are intended to be merely exemplary, and not to limit the scope of the invention — which is to be determined by reference to the appended claims.

WHAT IS CLAIMED IS:

1. Noninvasive apparatus for measuring blood-sugar concentration in a body by measuring electromagnetic-radiation reflectivity from the body; said apparatus comprising:

means for directing electromagnetic radiation to such body; and

means for receiving and measuring electromagnetic radiation reflected from such body substantially without spectral analysis of the reflected electromagnetic radiation.

2. The apparatus of claim 1 for use in measuring electromagnetic radiation reflectivity from an eye of such body, wherein:

the directing means direct electromagnetic radiation to such eye; and

the receiving and measuring means comprise means for receiving and measuring electromagnetic radiation reflected from such eye.

3. The apparatus of claim 1, wherein the receiving and measuring means comprise:

a monochrome detector array.

4. The apparatus of claim 3, wherein:

the monochrome detector array comprises a black-and-white CCD camera.

5. The apparatus of claim 4, wherein:

the receiving and measuring means comprise a digital processor for analyzing signals from the CCD camera.

6. The apparatus of claim 1, wherein:

the receiving and measuring means comprise a digital processor for analyzing signals representative of quantities of the reflected electromagnetic radiation.

7. The apparatus of claim 6, wherein:

the digital processor is part of a personal computer; and

the blood glucose level is reported on a monitor screen of the computer.

8. The apparatus of claim 6, wherein:

the apparatus is a handheld portable unit;

the unit comprises reporting means for indicating the blood glucose level; and

the digital processor is part of the handheld portable unit.

9. The apparatus of claim 8, wherein:

the reporting means comprise an LCD unit for visually indicating the blood glucose level.

10. The apparatus of claim 1, wherein:

the receiving and measuring means comprise means for detecting change in level of the reflected electromagnetic radiation and relating said change to blood-glucose concentration.

11. The apparatus of claim 1, wherein the receiving and measuring means comprise:

means for detecting change in level of the reflected electromagnetic radiation; and

means for reporting glucose concentration as a substantially monotonic response to reflected-electromagnetic-radiation level.

12. The apparatus of claim 1, wherein the detecting means comprise:

means for responding to reflected visible electromagnetic radiation.

13. The apparatus of claim 1, wherein the detecting means comprise:

means for responding to electromagnetic radiation in the yellow or yellow-green portion of the spectrum, or both.

14. The apparatus of claim 1, wherein:

the means for receiving and measuring substantially without spectral analysis comprise means for eliminating response to electromagnetic radiation in the red or infrared, or both.

15. The apparatus of claim 1, wherein:

the means for receiving and measuring substantially without spectral analysis do take into account a reverse signal response in the red or infrared, or both.

16. Noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from the body; said apparatus comprising:

a self-contained case;

means, mounted to the case, for directing electromagnetic radiation to such body; and

means, mounted to the case, for receiving and measuring electromagnetic radiation reflected from such body.

17. The apparatus of claim 16, wherein:

the case is fully portable.

18. The apparatus of claim 16, wherein:

the case fits in the palm of a normal-size adult's hand.

19. Noninvasive apparatus for measuring blood-sugar concentration in a body by measuring electromagnetic-radiation reflectivity from an eye of the body; said apparatus comprising:

means for directing electromagnetic radiation to an iris of such eye;

means for receiving and measuring electromagnetic radiation reflected from such iris; and

a programmed digital processor for analyzing the measured reflected radiation and computing blood-sugar concentration therefrom;

wherein the programmed processor comprises means for using a reflection of the electromagnetic-radiation source, from such eye, as a peak amplitude point for image alignment.

20. The apparatus of claim 19, wherein the receiving and measuring means also comprise means for receiving and measuring electromagnetic radiation from a pupil of such eye, for determination of:

a baseline dark level, or

an illumination level provided by the electromagnetic-radiation directing means, or

both said baseline dark level and said illumination level.

21. A blood-glucose measuring method comprising the steps of:

imaging forward surfaces of a person's eye on an electronic camera;

digitizing resultant image signals from the camera;

to determine blood-glucose level, processing pixel signals representing the iris, separately from pixel signals representing other parts of the eye.

22. The method of claim 21, further comprising the steps of:

processing pixel signals representing the pupil to obtain a baseline dark level or an illumination level, or both; and

applying the dark level or illumination level, or both, to refine the pixel signals representing the iris.

23. The method of claim 22, wherein the processing step comprises:

applying average reflected intensity level of the pupil to represent the dark level baseline.

24. The method of claim 21, wherein:

the iris-pixel signal processing comprises integrating all usable iris-pixel signals to produce a unitary intensity indication.

25. The method of claim 24, wherein:

the applying step comprises integrating into said indication only intensities that are higher than that of the pupil.

26. The method of claim 21, further comprising the step of:

substantially removing image scene and illumination variation.

27. The method of claim 21, further comprising the step of:

calibrating readings for an individual patient.

28. The method of claim 21, further comprising the step of:

masking out the pupil pixels from the iris region.

29. The method of claim 28, wherein:

the masking step comprises applying a software pupil mask that substantially stabilizes the number of iris pixels available for use and substantially stabilizes pupil centering within the iris image.

30. The method of claim 29, wherein:

the pupil mask is larger than the largest pupil diameter occurring in measurement conditions.

31. The method of claim 21, further comprising the step of:
masking out the pupil pixels from the iris region.

32. The method of claim 21, further comprising the step of:
diffusing source electromagnetic radiation to minimize hot spots.

33. The method of claim 21, further comprising the step of:
removing peak signal amplitudes, to minimize the effect of illumination hot spots.

34. The method of claim 21, further comprising the step of:
mapping illumination hot spots, to enable disregarding hot-spot regions in said processing step.

35. The method of claim 21, further comprising the step of:
adjusting image contrast to substantially fill the complete dynamic range of pixel data words.

36. The method of claim 21, further comprising the step of:
looking up the measured level in a lookup table to obtain a corresponding numerical blood-glucose concentration indication in quantity of glucose per unit blood volume.

37. The method of claim 21, wherein:
said digitizing step comprises distinguishing electromagnetic-radiation-intensity changes at least as small as one part in ten thousand.

38. The method of claim 21, comprising these steps:

finding a centroid of the pupil of the eye;

calculating average brightness around the pupil centroid;

masking out the pupil region of the eye;

equalizing the iris image using the pupil brightness as a level baseline;

removing hot spots if present;

integrating all of the processed iris pixels to obtain a numerical representation of brightness level of the iris;

searching a lookup table to apply a previously developed calibration and thereby determine an imputed glucose concentration in quantity of glucose per unit volume; and

displaying the imputed glucose concentration.

39. A blood-glucose measuring method for use with a small electromagnetic-radiation source and comprising the steps of:

automatically finding a reflection, from a patient's pupil, of the electromagnetic radiation; and

automatically performing a position alignment based upon the location of said reflection of the electromagnetic radiation.

40. The method of claim 39, further comprising the step of:

zeroing-out the area within the electromagnetic-radiation source, to form an image of forward surfaces of the eye without the electromagnetic-radiation source.

41. The method of claim 39, for use with a centrally disposed electromagnetic-radiation source and further comprising the step of:

growing a pupil mask, starting from the electromagnetic-radiation source as a centerpoint, to cover the pupil area in the image.

42. The method of claim 41, further comprising the step of:

capturing brightness level in an area under the aligned pupil mask for use in a dark-level calibration.

43. Apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from an eye of the body; said apparatus comprising:

a detector array;

a small electromagnetic-radiation source held directly in front of the detector array, for directing electromagnetic radiation to such eye; and

means for receiving and measuring electromagnetic radiation reflected from such eye.

44. The apparatus of claim 43, further comprising:

a lens between the detector array and the electromagnetic-radiation source.

45. The apparatus of claim 44, wherein:

the electromagnetic-radiation source shines toward the eye from substantially the geometric center of the lens.

46. The apparatus of claim 43, wherein:

the electromagnetic-radiation source shines toward the eye from substantially the effective geometric center of the array.

47. The apparatus of claim 46, further comprising:

means for using a reflection of the electromagnetic-radiation source, from such eye, as a peak amplitude point for finding the image center.

48. The apparatus of claim 43, for use in measuring blood glucose concentration for such body of a human being; and wherein:

the electromagnetic-radiation source is a visual centering target for the human being;

wherein, to take a measurement, the human being looks substantially directly toward the electromagnetic-radiation source.

49. Apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from blood of the body; said apparatus comprising:

means for directing electromagnetic radiation to such blood; and

means for receiving and measuring electromagnetic radiation reflected from such blood substantially without spectral analysis of the reflected electromagnetic radiation.

50. A noninvasive method for measuring intraocular pressure by measuring electromagnetic-radiation focal characteristics for forward surfaces of the eye; said method comprising the steps of:

finding focal distances to the inner and outer diameters of the iris respectively; and

interpreting discrepancy between said focal distances as a measure of said pressure.

FIG. 1

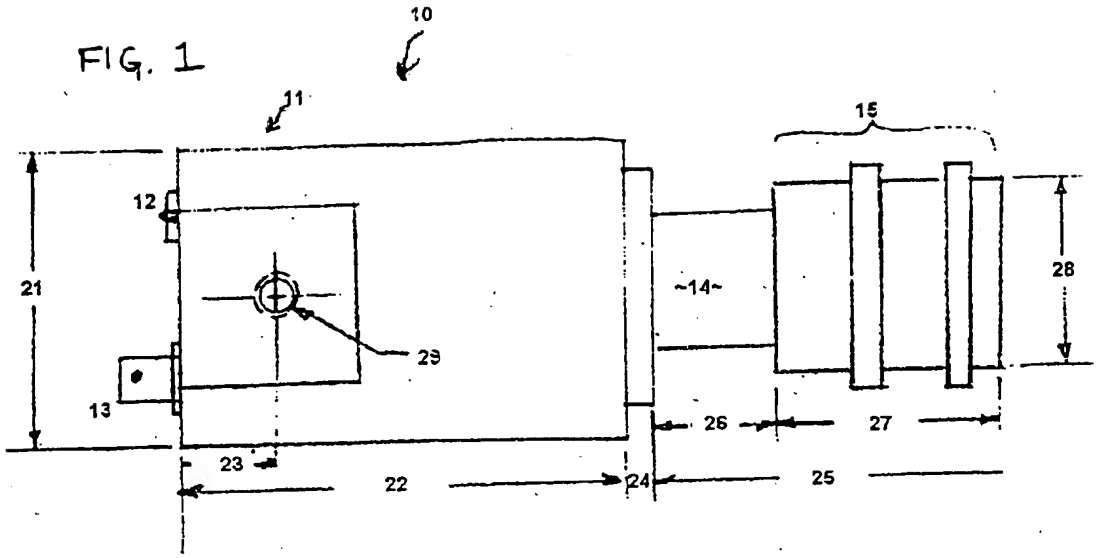

10
11
15
12
21
~14~
28
29
13
26
27
23
22
24
25

FIG. 2

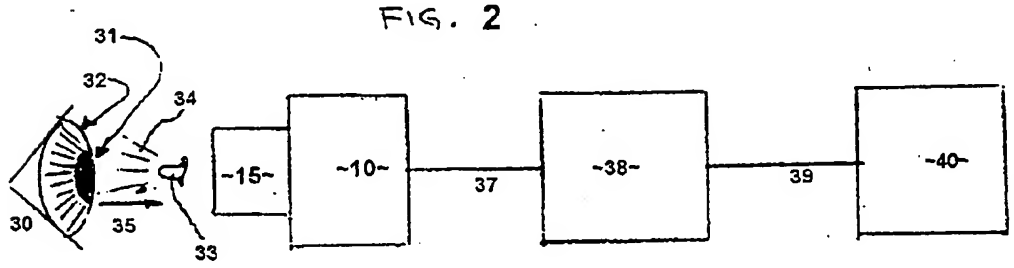

31
32
34
30
35
33
~15~
~10~
37
~38~
39
~40~

FIG. 3

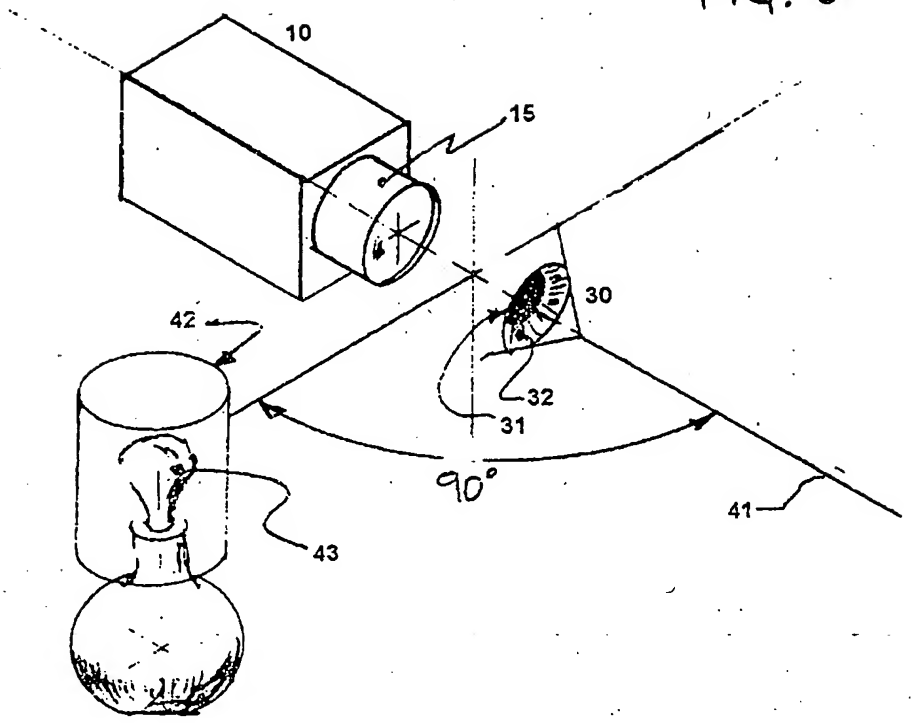


FIG. 4

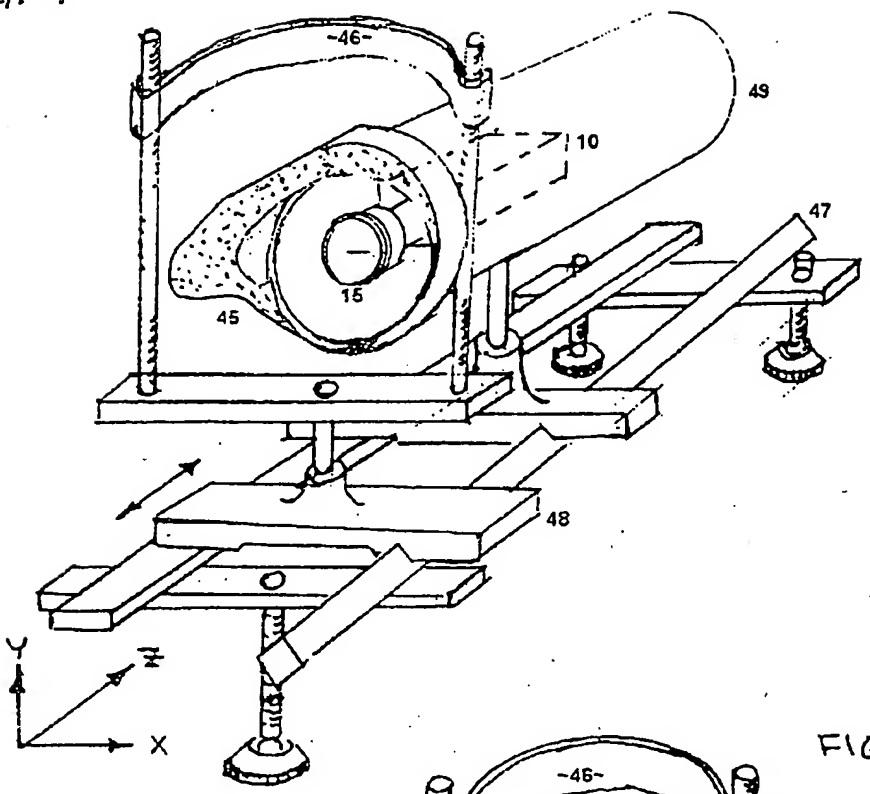


FIG. 5

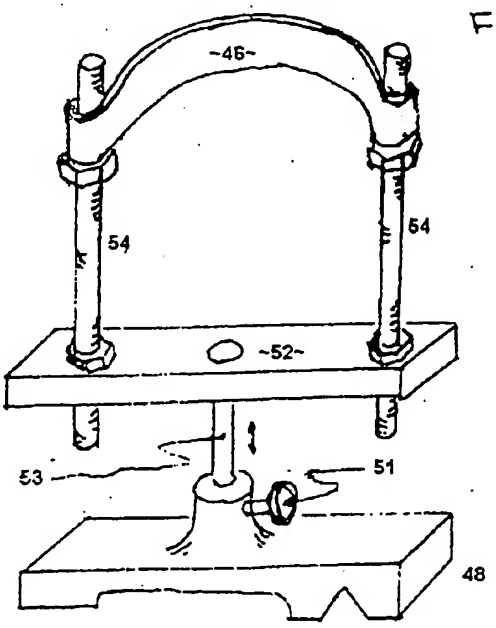


FIG. 6

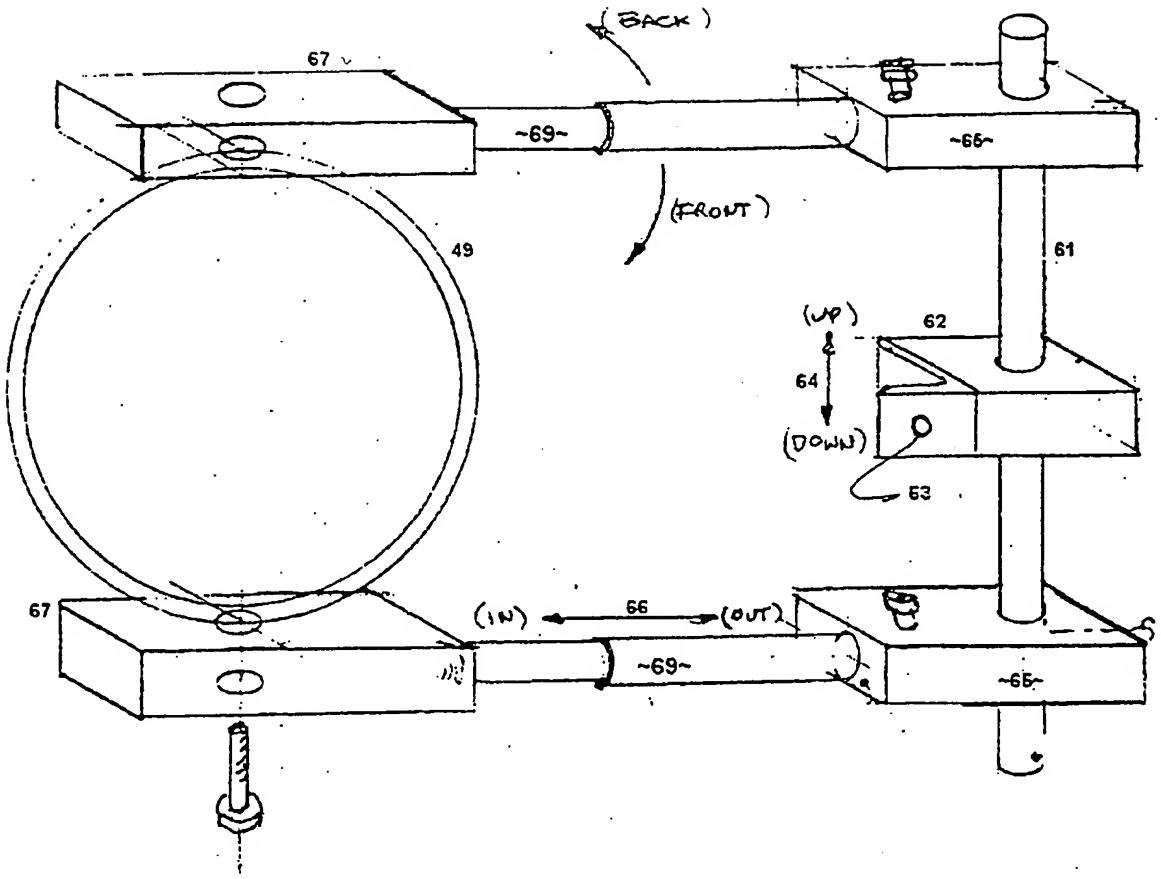


Fig. 7

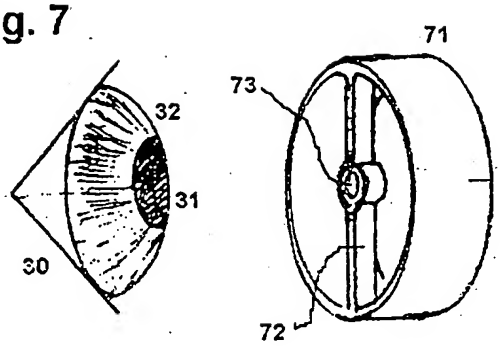


Fig. 8

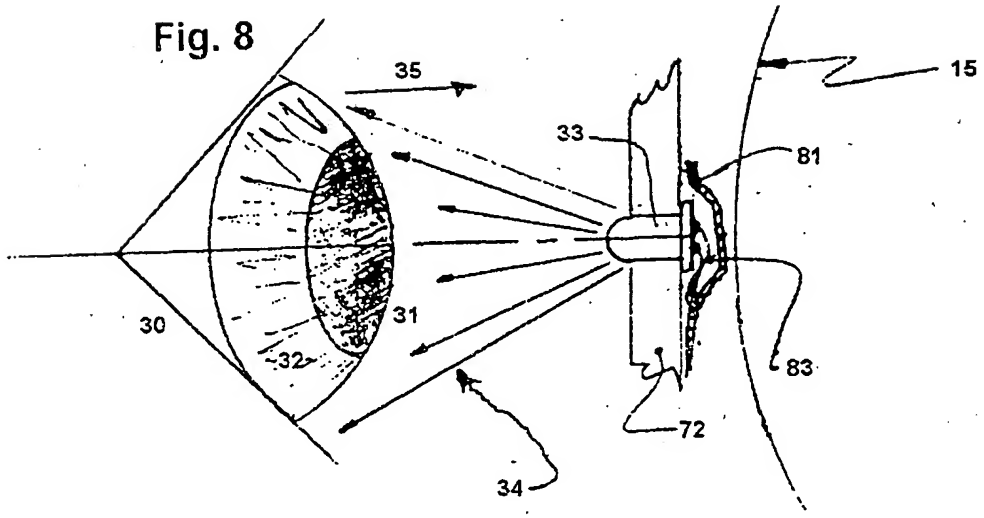


FIG. 9

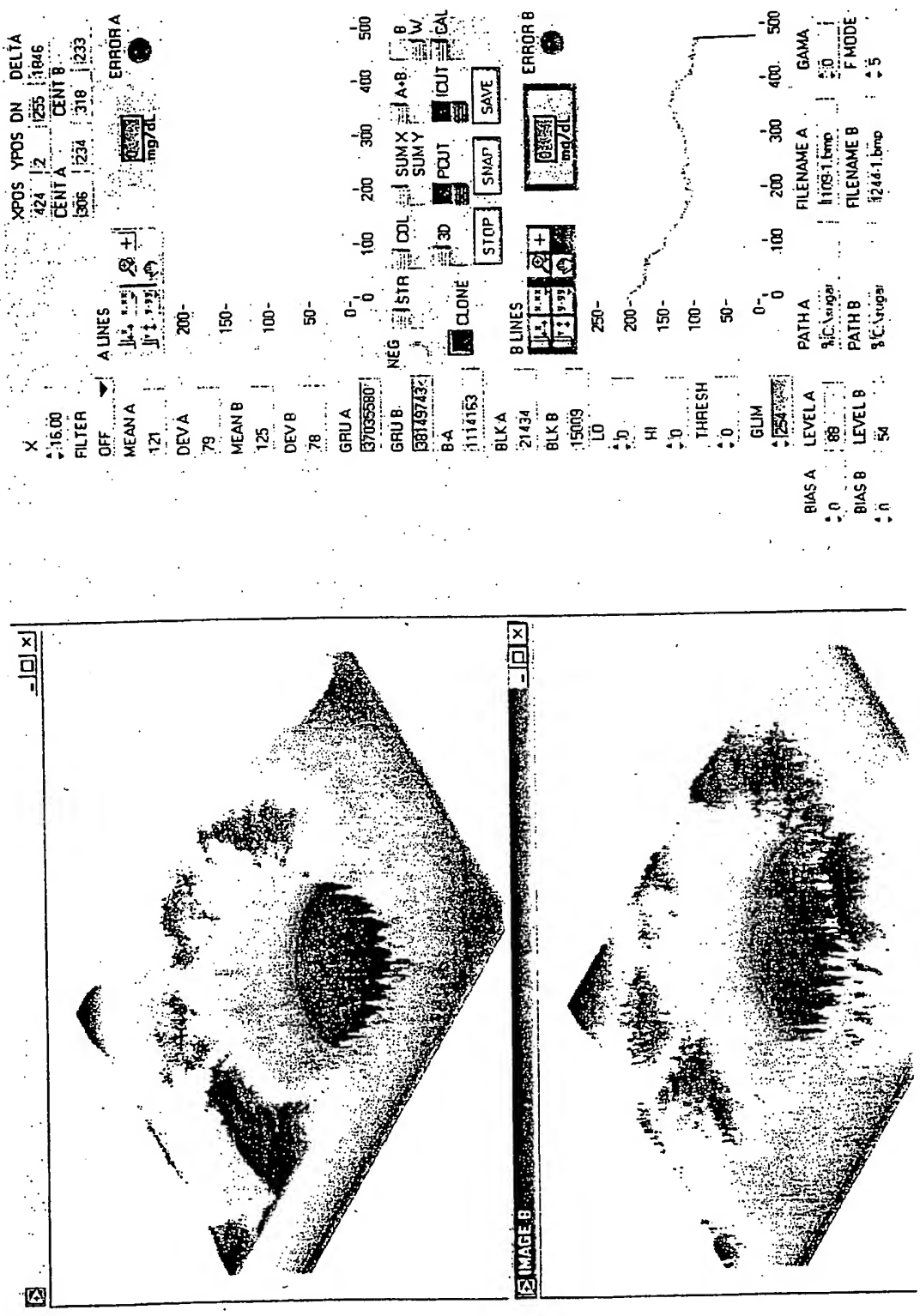

XPOS YPOS DN DELTA
424 2 255 1846
CENT A CENT B
306 234 318 233
A LINES
ERROR A
mg/dL
MEAN A
121
DEV A
79
MEAN B
125
DEV B
78
GRU A
37035580
GRU B
38149743
BA
1114163
BLK A
21434
BLK B
15009
LO
HI
THRESH
GLIM
254
PATH A
PATH B
LEVEL A
LEVEL B
BIAS A
BIAS B
B LINES
ERROR B
FILENAME A
FILENAME B
GAMA
F MODE
STOP
SNAP
SAVE
CLONE
COL
STR
NEG
3D
PCUT
ICUT
SUM X
SUM Y
A+B
IMAGE B

FIG. 10

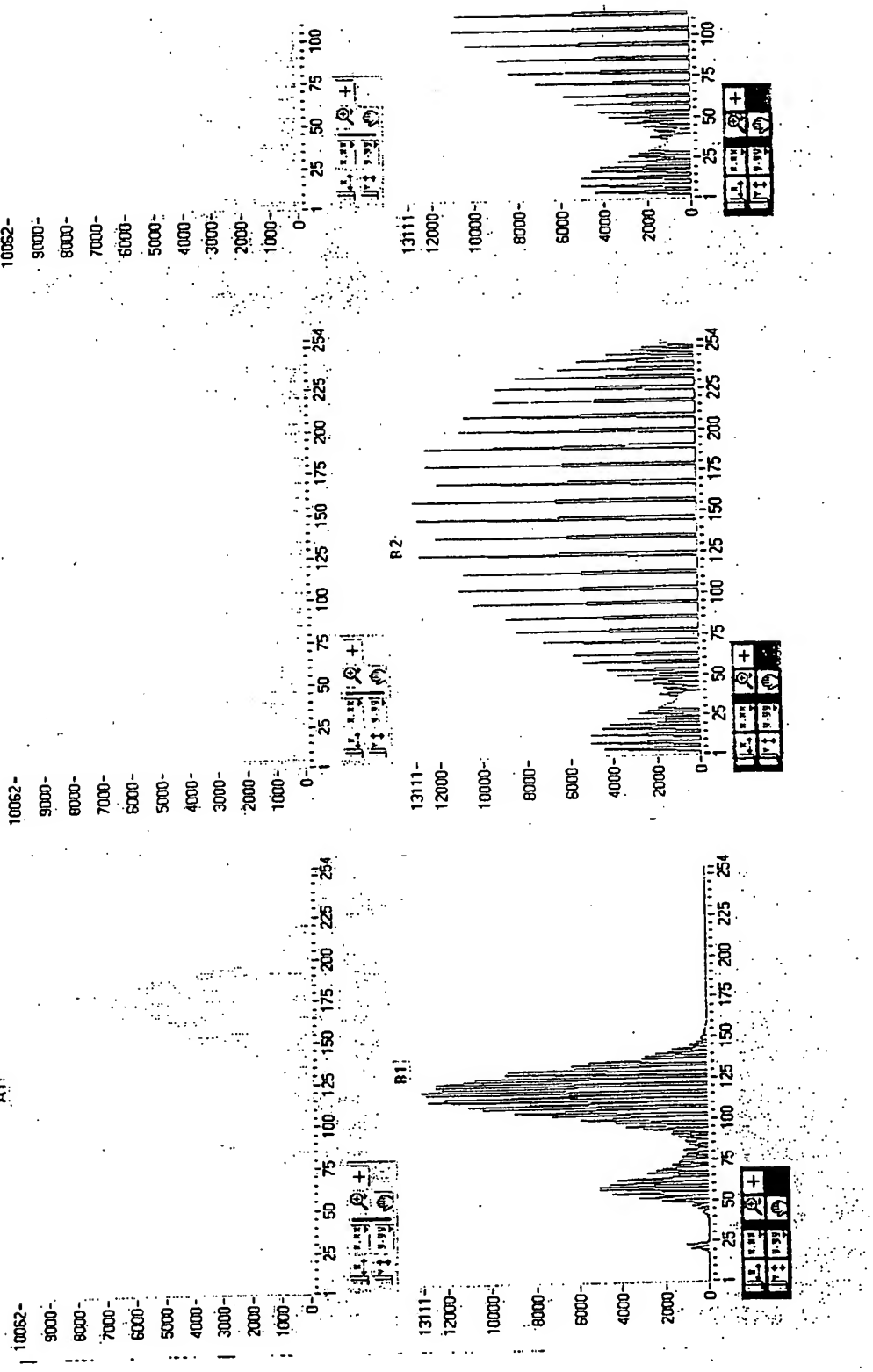
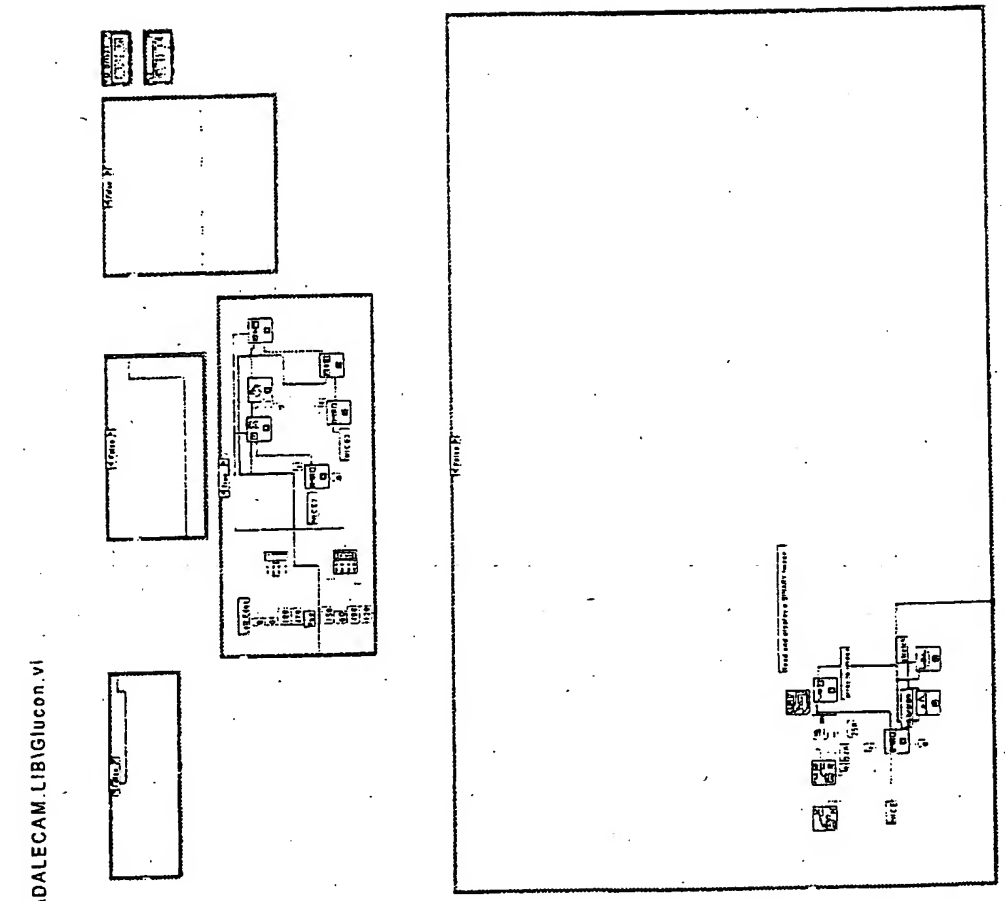


FIG 11



lucon.vi
:\LabVIEW5\DALECAM.LIB\lucon.vi

FIG 12

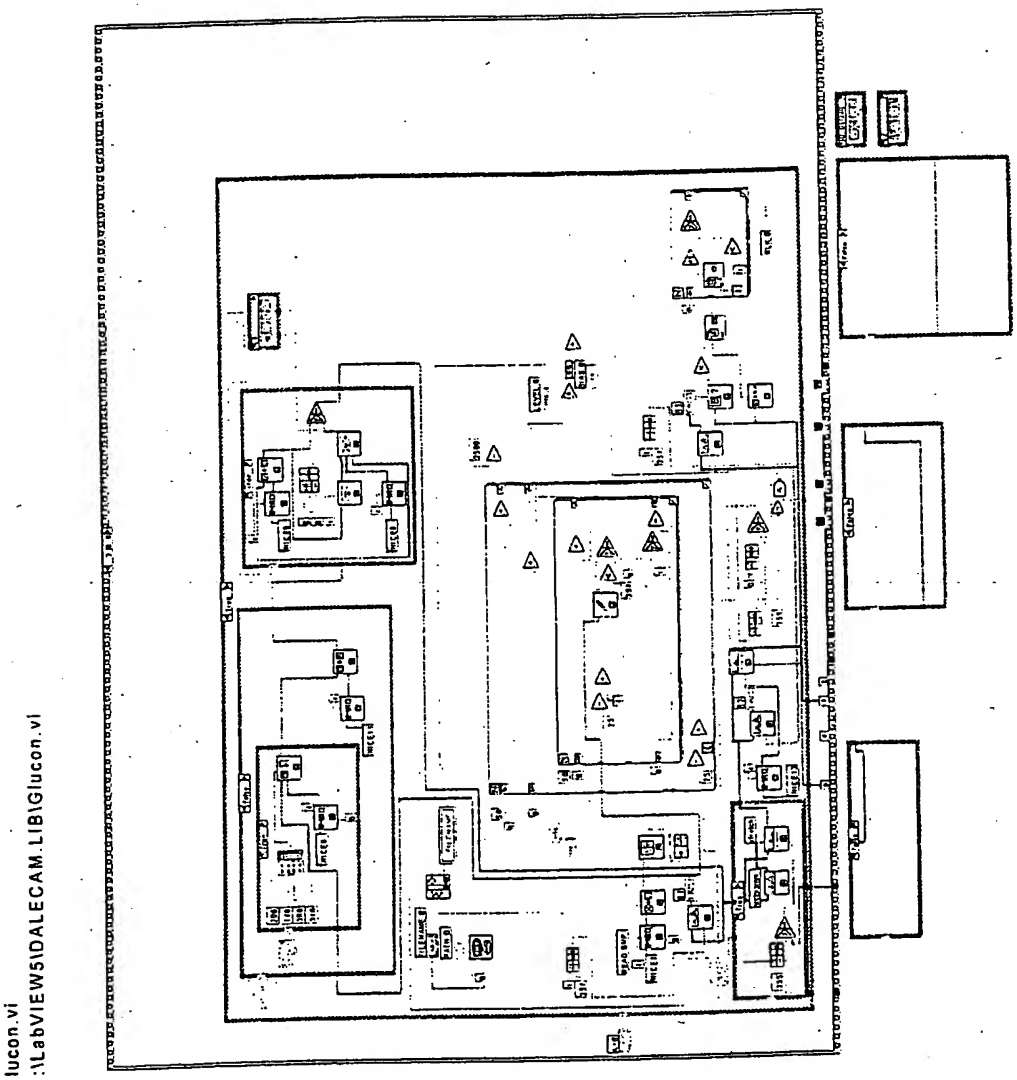


FIG. 13

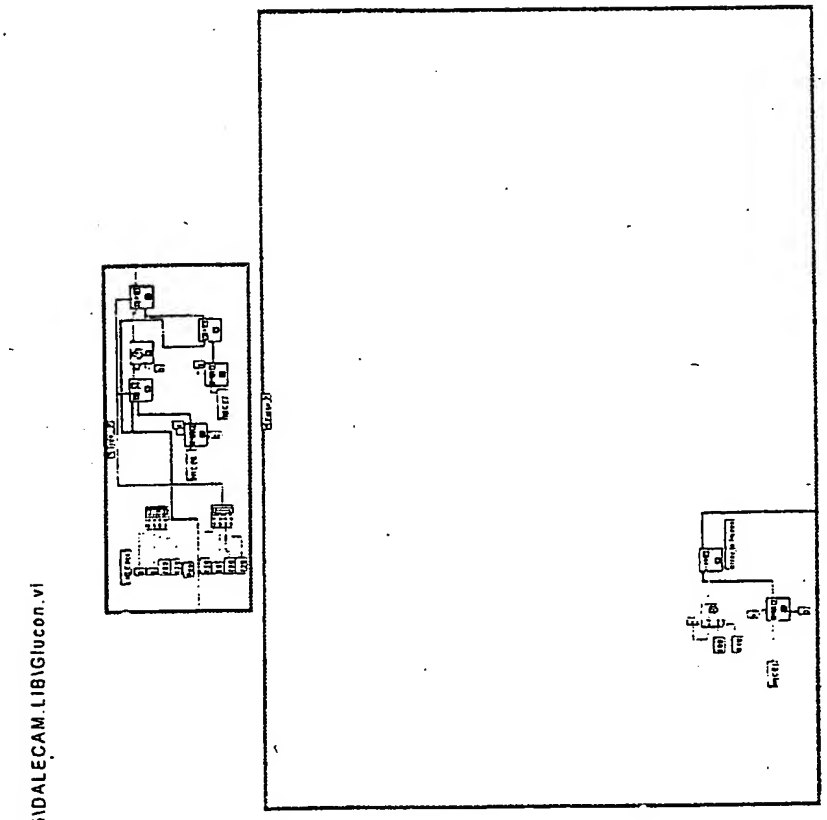


FIG. 14

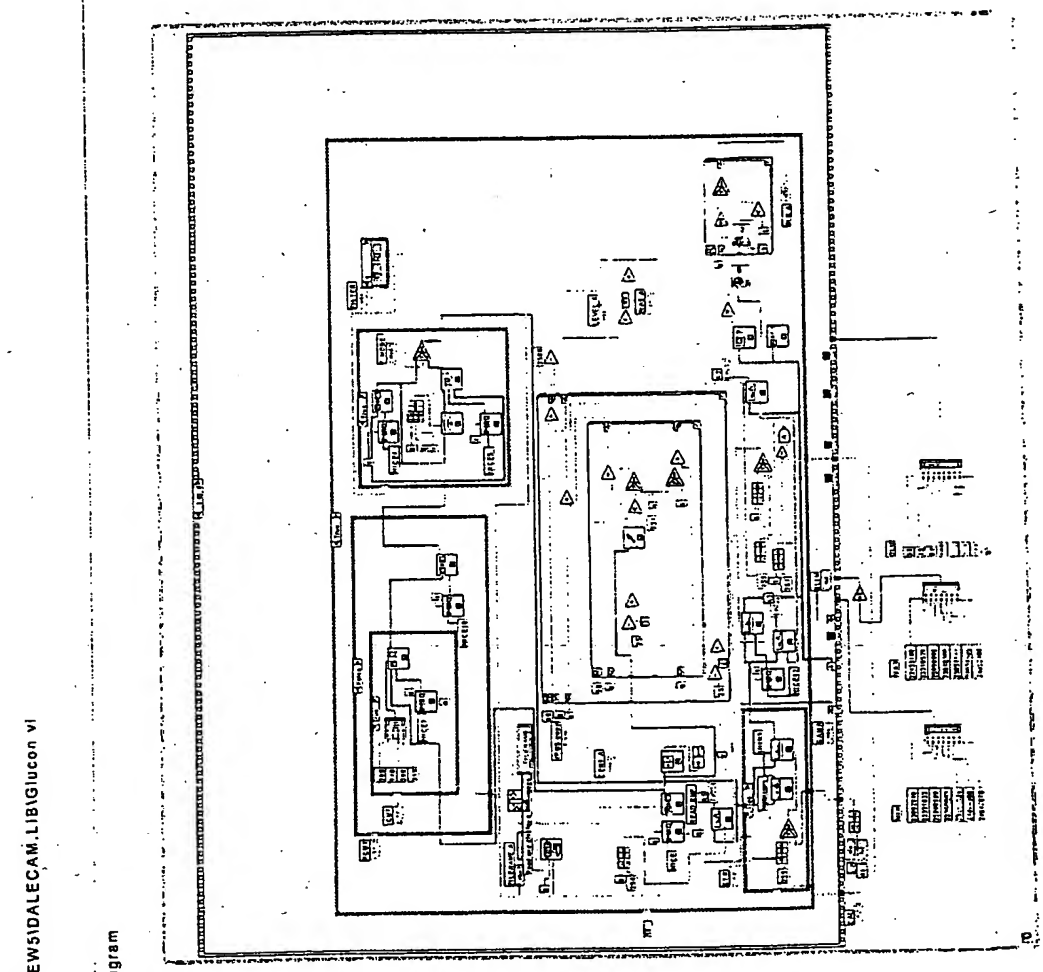


FIG.16

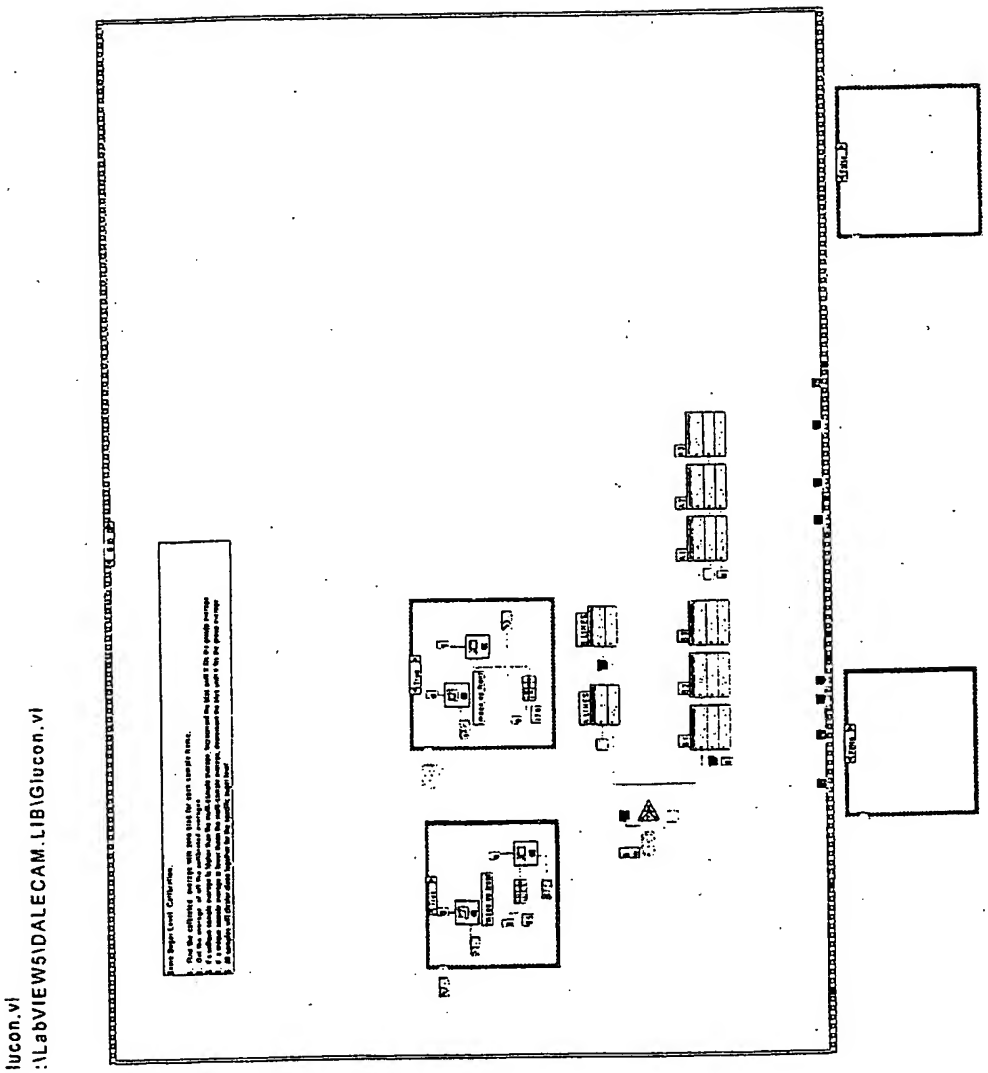
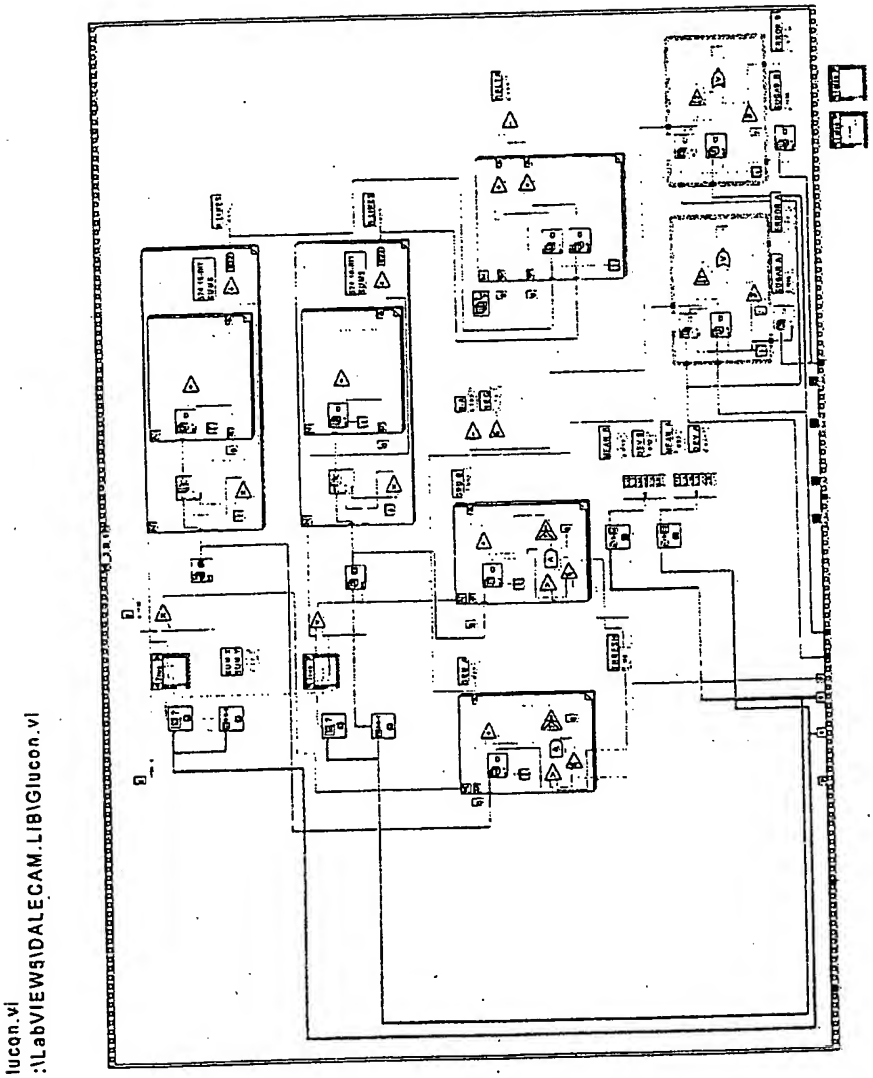


FIG. 14



lucon.vi
:\LabVIEW5\DALECAM.LIB\Glucon.vi

FIG. 17

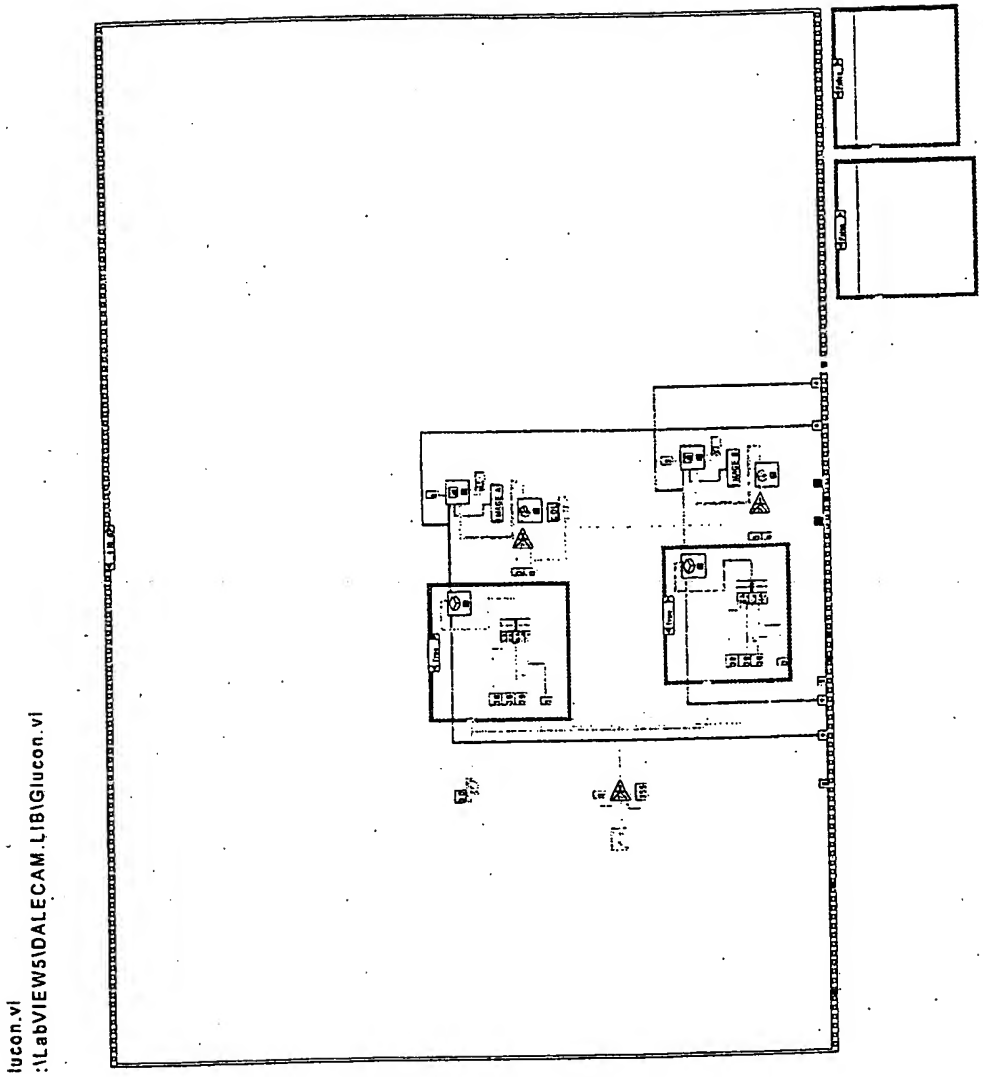
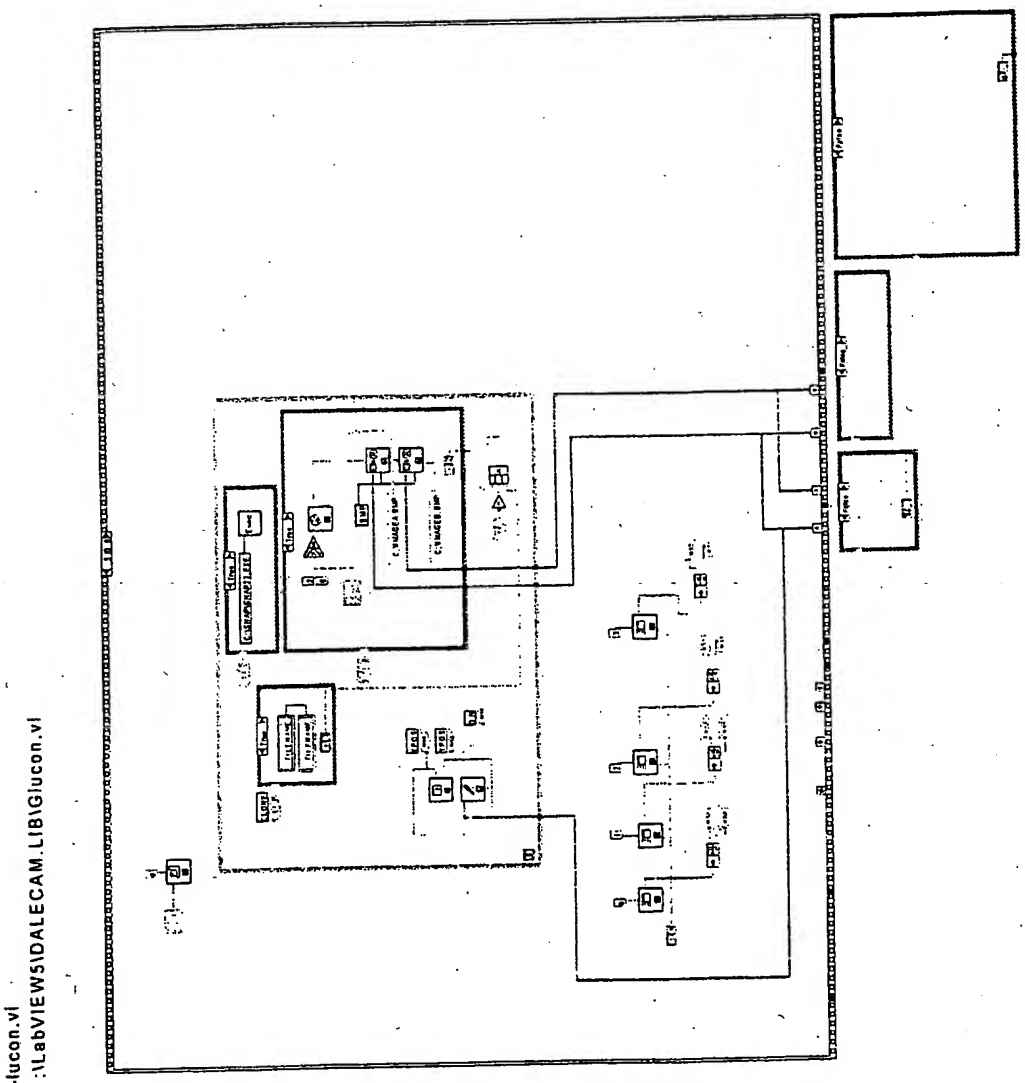


FIG 18



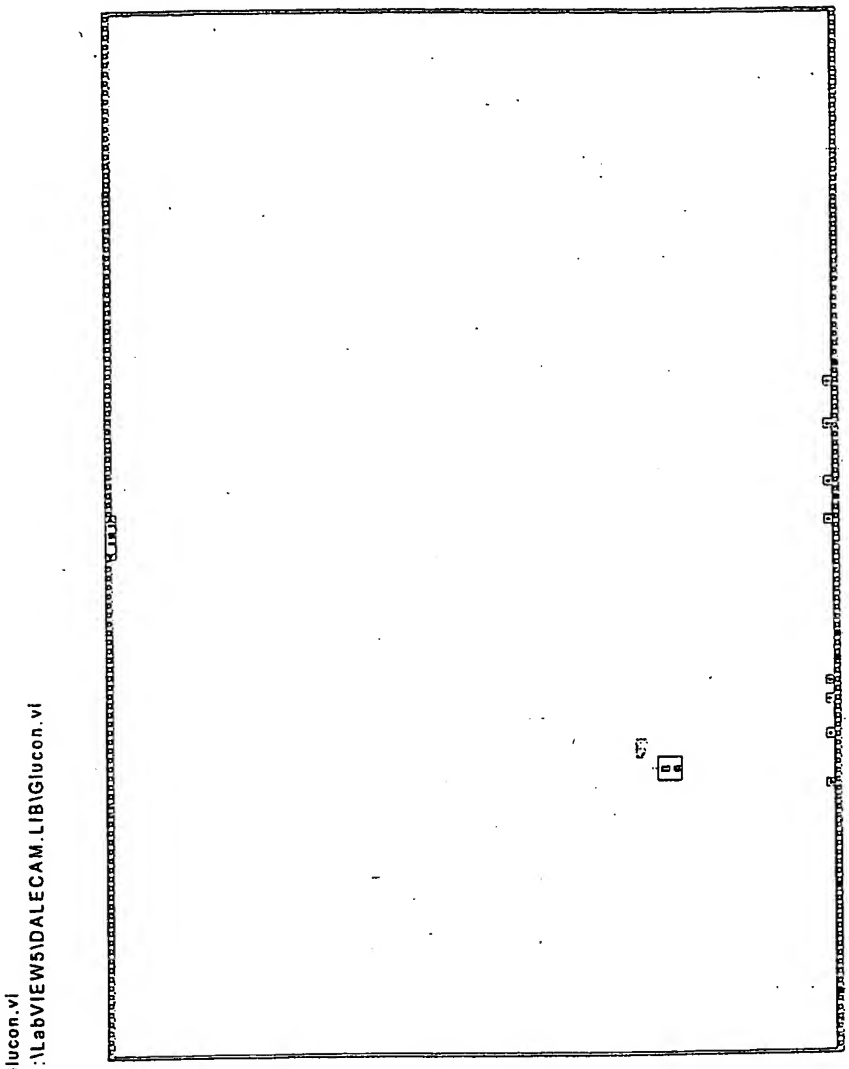
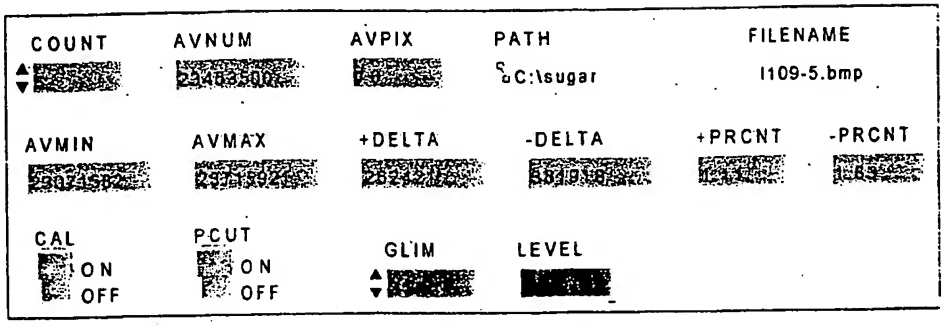


FIG. 19

FIG. 20

Average.vi
C:\LabVIEW5\DALECAM.LIB\Average.vi



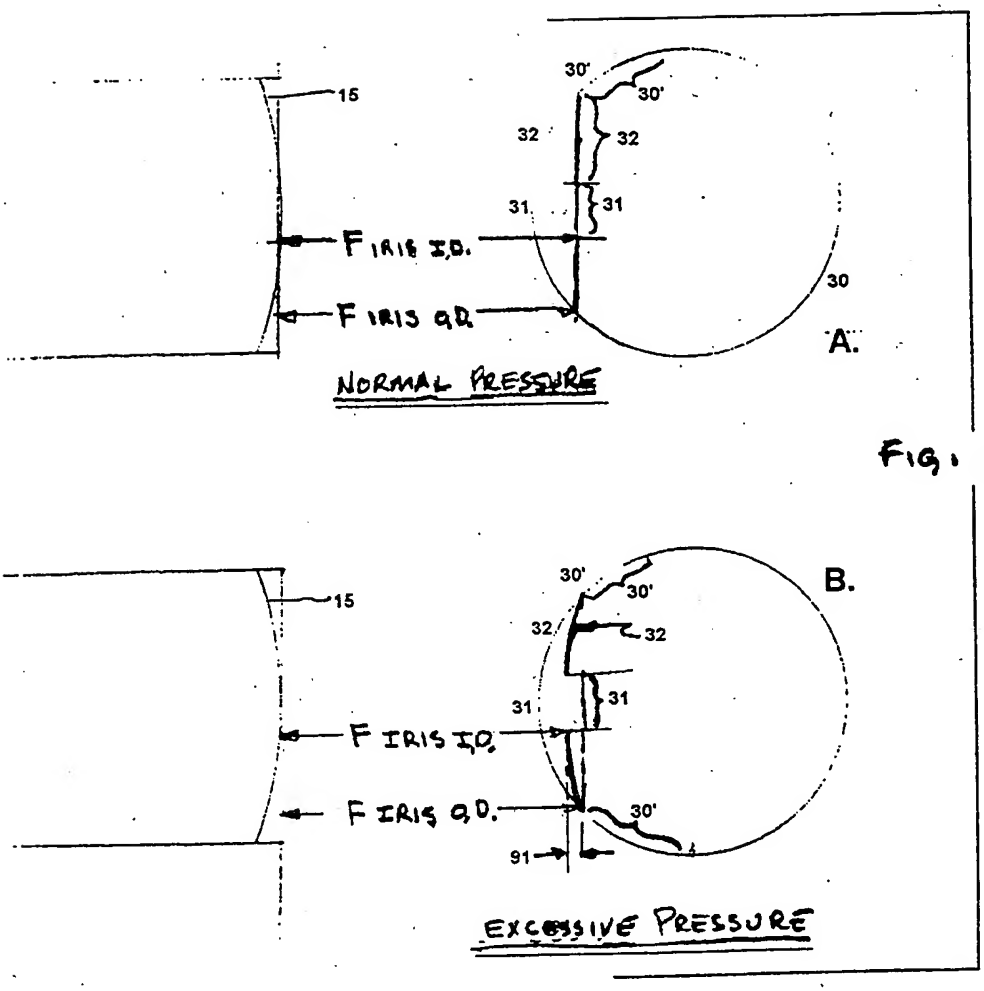
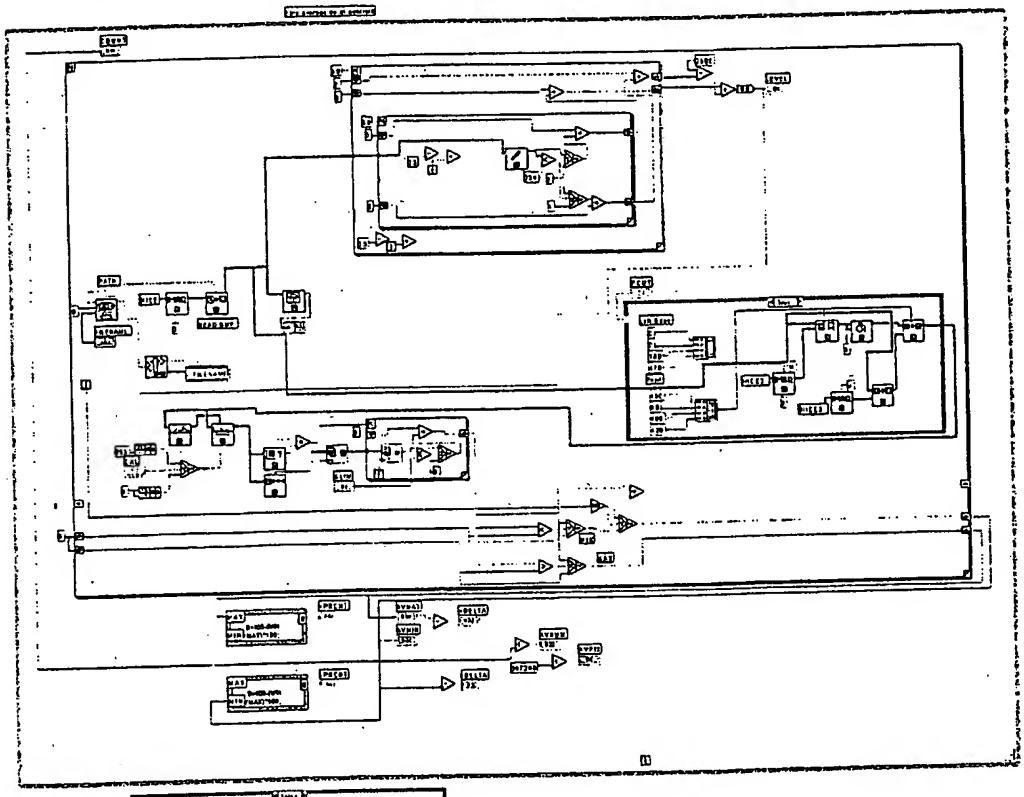

15
30'
30'
32
32
31
31
F IRIS I.D.
F IRIS O.D.
30
A.
NORMAL PRESSURE
B.
15
30'
30'
32
32
31
31
F IRIS I.D.
F IRIS O.D.
30'
91
EXCESSIVE PRESSURE

FIG. 23

Average.vi
C:\LabVIEW5\DALECAM.LIB\Average.vi

FIG. 21

Block Diagram



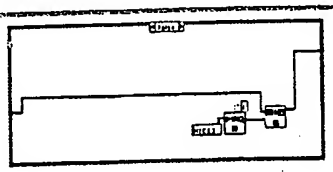


FIG. 22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21680

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/05
US CL :600/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/310, 316, 345, 347, 456, 365

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,569,186 A (LORD et al.) 29 October 1996, entire document.	1-50
A	US 5,329,931 A (CLAUSON et al.) 19 July 1994, entire document.	1-50

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 JANUARY 2000	10 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RYAN CARTER Telephone No. (703) 308-2990

Form PCT/ISA/210 (second sheet)(July 1992)

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/05

A1

(11) International Publication Number: WO 00/16692

(43) International Publication Date: 30 March 2000 (30.03.00)

(21) International Application Number: PCT/US99/21680

(22) International Filing Date: 17 September 1999 (17.09.99)

(30) Priority Data:
60/100,804 18 September 1998 (18.09.98) US

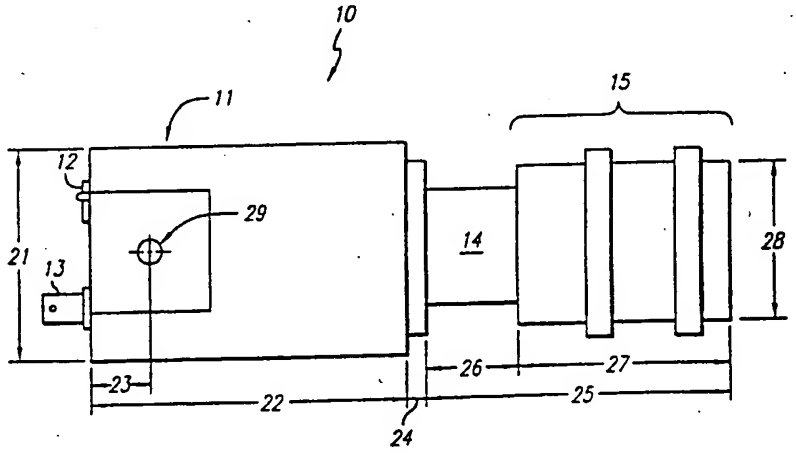
(71)(72) Applicants and Inventors: PRONIEWICZ, Walter, K. [US/US]; 3300 Barhite Street, Pasadena, CA 91107 (US). WINTHER, Dale [US/US]; 4745 Briggs, La Crescenta, CA 91214 (US).

(74) Agent: POPLAWSKI, Edward, G.; Pretty, Schroeder & Poplawski, LLC, 444 South Flower St., 19th Floor, Los Angeles, CA 90071 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NONINVASIVE MEASUREMENT OF BLOOD SUGAR BASED ON OPTOELECTRONIC OBSERVATIONS OF THE EYE



(57) Abstract

Electromagnetic radiation reflectivity from the body is measured. One form of the invention measures essentially without spectral analysis. The eye (30) is an advantageous part of the body for measurement. A monochrome detector array, e.g., black, and white CCD camera (10), suffices for the measurements. The apparatus detects changes in level of the reflected radiation, and relates the changes to glucose concentration. The relationship is monotonic as between glucose, and amount of reflected radiation. The system may operate with visible light, particularly in the yellow/green, or both; and may take into account a reverse signal response in the red IR, or both.

*(Referred to in PCT Gazette No. 28/2000, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NONINVASIVE MEASUREMENT OF BLOOD SUGAR BASED ON OPTOELECTRONIC OBSERVATIONS OF THE EYE

RELATED U. S. PATENT DOCUMENTS

This application claims priority of United States Provisional Patent Application serial 60/100,804 of Walter K. Proniewicz and Dale E. Winther, filed on September 18, 1998, and now wholly incorporated by reference into the present document. Except for a prior-patent listing and some commentary about prior art which appear below, this application is based substantially exclusively upon that provisional application and is accordingly believed to contain no new matter with respect to that application.

FIELD OF THE INVENTION

This invention relates generally to noninvasive blood testing; and more particularly to optoelectronic determination of glucose concentration in the blood, also called "blood sugar". Optoelectronic determination of glaucoma overpressure within the eye is also introduced.

BACKGROUND OF THE INVENTION

In various scientific and medical applications, blood testing is an invasive procedure, sometimes requiring blood to be drawn several times a day. This is true in particular for sufferers of diabetes — including one of the present inventors.

Existing methods use hypodermic syringes inserted into veins or arteries, and lancing devices for fingertips and

earlobes. With these methods, frequent blood testing is uncomfortable and even frightening, particularly for young children and the very ill — or those with collapsed veins.

Furthermore people with a chronic condition or illness often experience pain, infection, or loss of feeling due to scarring, as a result of frequent self-testing. These negative considerations discourage many from taking responsibility for their own illnesses, thus deterring them from enjoying a full, normal life.

After blood has been drawn and placed on an indicator strip, it can be analyzed for blood glucose by handheld devices that perform spectral analysis of the blood on the strip. Some of these devices are nominally subject to plus-or-minus twenty- or thirty-percent error, and it is commonplace for two such devices to report blood-sugar values differing by 80 mg/dL and more — even when the reported values are both well below 200 mg/dL.

Some United States patents, adduced by a professional searcher, that may be relevant to the present invention are 5,713,353; 5,572,596; 5,471,542; 5,433,197; 5,432,866; 5,291,560; 5,016,282; 4,641,349; 3,958,560; and 3,533,683.

Thus the blood-monitoring field has failed to provide methods for determining blood glucose and other blood constituents precisely, accurately, and without the pain, infection and other physiological and psychological detriments mentioned above. As can now be seen, prior art in this field is subject to significant problems, and have left room for considerable improvement.

SUMMARY OF THE DISCLOSURE

The present invention introduces such improvement. The invention has several facets or aspects which are usable independently — although for greatest enjoyment of their ben-

efits we prefer to use them together, and although some of them do have some elements in common.

In preferred embodiments of a first of its independent aspects, the invention is noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from the body. The apparatus includes some means for directing electromagnetic radiation to such body. For purposes of breadth and generality in discussion of the invention we shall refer to these means simply as the "directing means".

In addition the apparatus includes some means for receiving and measuring electromagnetic radiation reflected from such body substantially without spectral analysis of the reflected electromagnetic radiation. Again for generality and breadth we shall call these the "receiving and measuring means".

The foregoing may represent a description or definition of the first aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, this facet of the invention entirely eliminates need for piercing the body or otherwise obtaining blood samples, and so avoids the discomfort, fear and other detriments discussed above. Furthermore this aspect of the invention is advantageous in that it requires no elaborate spectral modulation, or multiple detectors for different wavelength regions, or dispersive elements — such as required to perform spectral analysis.

The absence of requirement for spectral analysis is a direct result of our very interesting discovery that electromagnetic radiation reflected from the iris bears a monotonic relationship (though different in different wavelength regions) to glucose concentration in the blood. In consequence, the apparatus is remarkably simple, economical and reliable.

Although the first major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the directing means direct electromagnetic radiation to an eye of the body; and the receiving and measuring means include some means for receiving and measuring electromagnetic radiation reflected from the eye.

Further preferably the receiving and measuring means comprise a monochrome detector array — and in this case still more preferably the monochrome detector array comprises a black-and-white charge-coupled-detector (CCD) camera. Another related preference is that the receiving and measuring means include a digital processor for analyzing signals from the CCD camera.

More generally, such a processor is desirable for analyzing signals representative of quantities of the reflected electromagnetic radiation. In this case one preference is that the digital processor be part of a personal computer, and the blood glucose level is reported on a monitor screen of the computer.

An alternative preference, however, is that the apparatus be a handheld portable unit, that the unit include reporting means for indicating the blood glucose level, and that the digital processor be part of the handheld portable unit. In this case preferably the reporting means include an LCD unit for visually indicating the blood glucose level.

Another basic preference is that the receiving and measuring means include some means for detecting change in level of the reflected electromagnetic radiation, and relating said change to blood-glucose concentration. Still another is that the receiving and measuring means include some means for detecting change in level of the reflected electromagnetic radiation — and also some means for reporting glucose concentration that varies substantially monotonically with reflected-electromagnetic-radiation level. Another general preference is that the detecting means

include some means for responding to reflected visible light — and, in this case, particularly to light in the yellow or yellow-green portion of the spectrum, or both.

Although the apparatus has been described as operating substantially without spectral analysis, this is not intended to imply that the apparatus is necessarily entirely unable to differentiate between spectral regions. For instance, preferably the apparatus includes some means for eliminating response to some particular electromagnetic-radiation band — e. g. the red or infrared, or both. Similarly the means for receiving and measuring substantially without spectral analysis preferably do take into account a reverse signal response in the red or infrared, or both.

Other preferences will appear in regard to this first aspect (and the others as well) of the invention, in the "DETAILED DESCRIPTION" section that follows.

In preferred embodiments of a second major independent facet or aspect, the invention is a noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from the body. The apparatus includes a self-contained case.

It also includes some means, mounted to the case, for directing electromagnetic radiation to the body. Also included are some means, mounted to the case, for receiving and measuring electromagnetic radiation that is reflected from the body.

The foregoing may represent a description or definition of the second aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, because we have established through prototype experimentation and testing that the entire invention is capable of reduction to be carried within a self-contained case, the many benefits of noninvasive measurement can be enjoyed in a unit that need not take the form of a

machine only suited for use in a medical facility. Rather, the invention can be implemented in a machine suited for patients' use at home, or at an ordinary office or other business — or in cars, restaurants, etc.

Although the second major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the case is fully portable. Also in this instance preferably the case fits in the palm of a normal-size adult's hand.

In preferred embodiments of a third of its major independent facets or aspects, the invention is a noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from an eye of the body. The apparatus includes some means for directing electromagnetic radiation to an iris of such eye. It also includes some means for receiving and measuring electromagnetic radiation reflected from such iris. Also included is a programmed digital processor that analyzes the measured reflected radiation and computing blood-sugar concentration therefrom — and in particular uses a reflection of the electromagnetic-radiation source, from the eye, as a peak amplitude point for image alignment.

The foregoing may represent a description or definition of the third aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, the eye is generally available for optoelectronic measurements without the subject's disrobing or any other great inconvenience. Moreover, condition of the blood in the eye is generally particularly rapid in its response to or tracking of the condition of the blood in other critical parts of the body — particularly the brain.

Although the third major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the receiving and measuring means also include some means for receiving and measuring electromagnetic radiation from a pupil of the eye.

This preference facilitates determination of a baseline dark level, or of an illumination level provided by the electromagnetic-radiation directing means, or both.

In preferred embodiments of a fourth of its major independent facets or aspects, the invention is a blood-glucose measuring method. The method includes the step of imaging forward surfaces of a person's eye on an electronic camera. It also includes digitizing resultant image signals from the camera. Further the method includes — to determine blood-glucose level — processing pixel signals representing the iris, separately from pixel signals representing other parts of the eye.

The foregoing may represent a description or definition of the fourth aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, analysis of conditions in the iris is advantageous in that the iris exhibits monotonic relationships (peculiar to different wavelength regions) between reflected electromagnetic-radiation level and glucose concentration — enabling enjoyment of the previously mentioned benefits of measurement without spectral analysis.

Furthermore the separation of iris and pupil signals for processing is amenable to straightforward implementation based upon geometry, leading to easy compensation for varying illumination level and the like as previously mentioned.

Although the fourth major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the method also includes the steps of processing pixel signals representing the pupil to obtain a baseline dark level or an illumination level, or both — and also applying the dark level or illumination level, or both, to refine the pixel signals representing the iris. In this case advantageously the processing step includes applying an average reflected intensity level of the pupil to represent the dark level baseline.

Another general preference is that the iris-pixel signal processing comprises integrating all usable iris-pixel signals to produce a unitary intensity indication. In this case preferably the applying step includes integrating into the indication only intensities that are higher than that of the pupil.

Yet another basic preference is to include the step of substantially removing image scene and illumination variation. Still another preference is to include the step of calibrating readings for an individual patient.

Another general preference is to include masking out the pupil pixels from the iris region. In this case the masking step also preferably includes applying a software pupil mask that substantially stabilizes the number of iris pixels available for use, and substantially stabilizes pupil centering within the iris image. Further if this is done preferably also the pupil mask is larger than the largest pupil diameter occurring in measurement conditions.

Other general preferences relative to the method of our invention include these steps, considered individually:

- masking out the pupil pixels from the iris region;

- diffusing source electromagnetic radiation to minimize hot spots;

- removing peak signal amplitudes, to minimize the effect of illumination hot spots;

- mapping illumination hot spots, to enable disregarding hot-spot regions in said processing step;

- adjusting image contrast to substantially fill the complete dynamic range of pixel data words;

- looking up the measured level in a lookup table to obtain a corresponding numerical blood-glucose concentration indication in quantity of glucose per unit blood volume; and

- said digitizing step comprises distinguishing electromagnetic-radiation-intensity changes at least as small as one part in ten thousand.

Another preference, still as to the fourth (method) aspect of our invention, is this sequence of steps:

- finding a centroid of the pupil of the eye;
  calculating average brightness around a pupil centroid;
- masking out the pupil region of the eye;
- equalizing the iris image using the pupil brightness as a level baseline;
- removing hot spots if present;
- integrating all of the processed iris pixels to obtain a numerical representation of brightness level of the iris;
- searching a lookup table to apply a previously developed calibration and thereby determine an imputed glucose concentration in quantity of glucose per unit volume; and
- displaying the imputed glucose concentration.

In preferred embodiments of a fifth major independent facet or aspect, the invention is a blood-glucose measuring method for use with a small electromagnetic-radiation source. This method includes the step of automatically finding a reflection, from a patient's pupil, of the electromagnetic radiation.

The method also includes the step of automatically performing a position alignment based upon the location of the reflection of the electromagnetic radiation. The foregoing may represent a description or definition of the fifth aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, this mode of operation very easily resolves several otherwise knotty problems of alignment, which can otherwise threaten the integrity of the overall measurement process — since the process is sensitive to alignment and control of signal returns from the white of the eye as well as the pupil.

Although the fifth major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the method also includes zeroing-out the area within the electromagnetic-radiation source, to form an image of forward surfaces of the eye without the electromagnetic-radiation source.

Another preference, especially when the method is for use with a centrally disposed electromagnetic-radiation source, is the step of growing a pupil mask — starting from the electromagnetic-radiation source as a centerpoint — to cover the pupil area in the image. In this case, preferably the method also includes capturing brightness level in an area under the aligned pupil mask, for use in a dark-level calibration.

In preferred embodiments of a sixth major independent facet or aspect, the invention is apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from an eye of the body. This apparatus includes a detector array.

It also includes a small electromagnetic-radiation source held directly in front of the detector array, for directing electromagnetic radiation to the eye. In addition the apparatus has some means for receiving and measuring electromagnetic radiation reflected from the eye.

The foregoing may represent a description or definition of the sixth aspect or facet of the invention in its broadest or most general form. Even as couched in these broad terms, however, it can be seen that this facet of the invention importantly advances the art.

In particular, use of a source in the described position greatly simplifies, in several ways, the processing of data derived from the optical system. Some specific benefits will be seen in the preferred implementations discussed immediately below and in the later "DETAILED DESCRIPTION" section of this document.

Although the sixth major aspect of the invention thus significantly advances the art, nevertheless to optimize enjoyment of its benefits preferably the invention is practiced in conjunction with certain additional features or characteristics. In particular, preferably the apparatus also includes a lens between the detector array and the electromagnetic-radiation source.

In this case, it is preferred that the electromagnetic-radiation source shine toward the eye from substantially the geometric center of the lens — or, alternatively of the detector array. In this case the apparatus further includes some means for using a reflection of the electromagnetic-radiation source, from the eye, as a peak amplitude point for finding the image center.

A more general preference, still as to this sixth main aspect of the invention — and especially when the apparatus

is for use in measuring blood-glucose concentration for the body of a human being — is that the electromagnetic-radiation source serve as a visual centering target for the human being. In such a system, the human being looks substantially directly toward the electromagnetic-radiation source to, in substance, automatically align or center (at least approximately) the pupil in the optical field.

In preferred embodiments of a seventh major independent facet or aspect, the invention is apparatus for measuring blood-sugar concentration in a living body, by measuring electromagnetic-radiation reflectivity from blood of the body. The apparatus includes some means for directing electromagnetic radiation to the blood.

It also includes some means for receiving and measuring electromagnetic radiation reflected from the blood substantially without spectral analysis of the reflected electromagnetic radiation. From all the discussion, in this document, of aspects of the invention, those skilled in the field of noninvasive medical instrumentation will understand that the invention operates, in one way or another, based upon presence of the blood in the iris or elsewhere within the body — thereby making the blood available for optoelectronic measurement. Accordingly the invention is not limited to the implementations expressly set forth.

All the foregoing operational principles and advantages of the present invention will be more fully appreciated upon consideration of the following detailed description, with reference to the appended drawings (not to scale), of which:

///

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a somewhat schematic diagram, in plan, of an experimental prototype CCD camera assembly used in preferred embodiments of the invention, and contemplated for adaptation into a commercial unit;

Fig. 2 is a block diagram showing the image input data stream derived from optoelectronic measurements of an eye, using the Fig. 1 camera assembly in a central-illumination arrangement;

Fig. 3 is an isometric view of a representative earlier prototype illumination geometry — one of several attempted, illustrating a diffuse-illumination approach;

Fig. 4 is a like view of a prototype optical bench, particularly including a foam ocular and a forehead rest;

Fig. 5 is a like but more detailed view of the Fig. 4 rest;

Fig. 6 is a like view of an early prototype eye-tracking system;

Fig. 7 is a like view of an early prototype bezel for mounting at the front of the camera lens and for aiming a small electromagnetic-radiation source toward the eye;

Fig. 8 is an enlarged view of the Fig. 7 bezel, shown with electromagnetic-radiation source and eye, in longitudinal elevation generally along the system centerline;

Fig. 9 is an image of part of a representative operator control panel, seen on a computer screen of our prototype apparatus while the system is imaging a subject eye;

Fig. 10 is a like image of another part of the same control panel display, particularly showing histograms representing results of different processing stages within the program;

Figs. 11 through 19 are a G program listing (graphical programming, as explained below) of the digital-processor code that produces output values in "arbits" (arbitrary units) related to glucose concentration;

Fig. 22 is an image like Figs. 9 and 10, but for another display of a control panel — for a second program,

used to correlate arbit values with an actual amount of patient blood sugar in conventional units;

Figs. 21 and 22 represent two pages of G code that represent the entire second program used to obtain calibrated IDN-to-glucose data as just mentioned; and

Fig. 23 is a diagrammatic showing of focal-distance measurements that can be used to determine glaucoma pressure automatically with apparatus analogous to certain forms of the glucose-concentration measuring systems described herein. View A represents a normal-pressure condition, and view B an abnormal or overpressure condition.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

1. OVERVIEW

A method has been found to determine the amount of blood sugar without the need for invasive procedures. This technique can determine sugar levels by analyzing reflected electromagnetic-radiation information from the eye.

The process uses a black & white CCD TV camera and a personal computer. A fully portable version that fits in the palm of one's hand is presently possible.

The combined result of the camera/computer arrangement is a numeric output that displays blood-glucose levels in units of milligrams/deciliter, on a computer screen or small LCD display. A handheld illumination and imaging system is used to take blood sugar measurements.

The system operates by integrating the reflected electromagnetic radiation from the iris portion of the eye — not from the retina. Numerous anterior blood vessels present a means of directly observing bloodstream content with exterior optical methods.

Glucose accumulations in this area produce a change in the intensity of reflected electromagnetic radiation. The

more sugar present, the higher the level of reflected electromagnetic radiation.

This change in electromagnetic-radiation reflection is too small to be seen with normal observation methods. The ability to measure electromagnetic-radiation intensity changes as small as 1 part in 10,000 is required to detect blood sugar changes.

The CCD camera images the eyeball and the image is digitized. These data are processed to remove the pupil pixels. Only the iris pixels are used as representative of glucose values as such, but as explained elsewhere the pupil pixels are used to develop baseline and illumination levels.

The iris pixels are integrated (summed) to produce a single intensity number. We sometimes call this the "integrated data number" or IDN for short; it is interchangeably designated "GLU", for glucose value.

The IDN (or GLU) value can be calibrated by removing image scene and illumination discrepancies. It can be further calibrated to an individual patient to produce an extremely accurate IDN-to-blood-sugar correlation. Repeatable scene geometry is also very desirable for accurate measurements.

2. MASKING AND NORMALIZATION

As mentioned above, the primary IDN calibration technique uses pupil reflection and geometry data. Changes in input electromagnetic-radiation levels are detected by sensing pupil brightness.

The average reflected intensity level of the pupil is used as the dark-level baseline for IDN processing. Only intensities that are higher than that of the pupil are integrated into the IDN.

This is a scene-to-scene automatic electromagnetic-radiation level calibration. If the scene electromagnetic-radiation level goes up, so do the levels of the pupil and the iris.

The pupil level offsets the higher iris level and preserves the scene-to-scene relative brightness. This guarantees that only sugar-level increases will cause measured intensity increases.

A further problem involves changes in pupil diameter and pupil centering within the scene. If these components are not held constant, the total number of iris pixels available for integration will change.

To control these effects, a software pupil mask is employed. This zeroes-out a fixed region around the pupil. It is larger than the largest pupil diameter and covers pupil-centering errors.

Some iris pixels are zeroed in the process, but all image frames are treated in the same way. The pupil mask is always the same size, and therefore all image frames contain the same number of iris pixels. The geometric distortions due to pupil variations are eliminated.

Another source of error is produced from illumination hot spots. Good electromagnetic-radiation source diffusion is needed to prevent the problem.

Hot-spot removal can be partially accommodated with software. Peak signal amplitudes are removed before the integration process. In addition, Hot Spot mapping can be used to extract the troublesome regions prior to integration.

Image contrast equalization (stretch) is also applied. This causes pixels to fill the complete dynamic range of pixel data words.

The pupil baseline data is applied to this process, permitting only the pixels that are brighter than the pupil to be remapped. As a result, further processing takes place using data that have been scene-level-biased and equalized to a full amplitude range.

3. CALIBRATION AND READOUT

The process of converting the IDN to a true glucose measurement requires a simple lookup operation to verify that the result is within a predetermined error band. The correlation from IDN to milligrams per deciliter (mg/dL) can be seen in the following formula.

$$IGN = \frac{IDN_{max} - IDN_{min}}{GL_{max} - GL_{min}} \cdot GL + IDN_{min}.$$

These terms are defined as follows.

IGN = implied glucose number

IDN_{max} = highest possible IDN (integrated data number)

IDN_{min} = lowest possible IDN

GL_{max} = highest possible glucose value (in mg/dL)

GL_{min} = lowest possible glucose value (mg/dL)

GL = actual glucose value (mg/dL)

Inserting a milligram/deciliter value in GL yields its equivalent IDN value in IGN.

Going from IDN to GL is accomplished by searching or hashing a lookup table. When the IDN value is equal or almost equal to a bounded IDN table value, GL is retrieved from the table and output as the glucose reading.

The IDN lookup table is produced by averaging multiple calibrated IDN samples for known glucose values. A fixed error range is based on a plus-or-minus deviation percentage from the average IDN.

This is done for all available glucose numbers. Because it is difficult to obtain values for every glucose number, values between known samples can be interpolated to create a complete table.

4. PROCESSING STEPS

These are the discrete processes performed by our prototype systems:

- image the eyeball
- find the centroid of the pupil
- calculate the average brightness around the pupil centroid
- mask out the pupil region of the eye
- equalize the iris image using the pupil brightness as a level baseline
- remove hot spots if present
- integrate all of the processed iris pixels
- search a lookup table to find the closest IDN-to-GL match
- display the imputed glucose number in GL

5. IMAGE INPUT PROCESSING

To reduce the complexity of the image-input system, software has been developed to optimize camera positioning and illumination consistencies. We have constructed an apparatus that holds a electromagnetic-radiation source directly in front of the camera lens.

The electromagnetic radiation is made to shine onto the eye from the geometric center of the lens. This results in even illumination of the eye, eliminating reflections and hot spots.

Two additional effects are created by this central-illumination geometry:

- the electromagnetic-radiation source becomes a visual centering target for the patient; and

- the electromagnetic-radiation source becomes a peak amplitude point for finding the image center.

The software finds the electromagnetic radiation (seen as a hot spot in the center of the pupil) and performs a position alignment based on its location.

Having found the center of the pupil, the software also performs the following processes.

- zero-out the area within the electromagnetic-radiation source, to eliminate the electromagnetic-radiation source from the pupil image

- determine the eye registration within the camera frame, and calculate the useful image area

- grow a pupil mask from the electromagnetic-radiation-source centerpoint and use it to cover the pupil area in the image

- capture the area under the aligned pupil mask for the dark-level calibration

Additional system sensitivity and accuracy can be obtained by capturing multiple frames and summing their IDNs together. Changes due to small movements of the eye are thereby averaged out. Digitally summed IDNs also increase effective integration time, resulting in a larger dynamic range.

6. WAVELENGTH EFFECTS

It has been observed that most visible light colors work well for glucose detection. Peak response appears to be in the yellow and yellow/green portion of the spectrum for the algorithm described above.

A reverse signal response takes place with near infrared illumination. The higher the glucose level, the lower the reflected electromagnetic-radiation.

This reverse effect can also be seen in the red region of the visible spectrum and can disturb the linearity of the glucose response. If the visible portion of the spectrum is used for the measurement, then using LED light sources that contain little or no red or infrared components improves measurement accuracy.

It is reasonable to generalize the foregoing observations, however, though this is not mentioned explicitly in our provisional application, to note what is common to both wavelength regions — i. e. that the level response is substantially monotonic, namely either an increasing function or a decreasing function for the different wavelength regions respectively.

The infrared reverse effect can be used to improve system accuracy. Infrared illumination yields a nonlinear conversion that produces a large dynamic range in the low-sugar region. This information can be processed for enhanced low-end performance.

A combination of visible and infrared processing can be done to produce dual response tables. These "inverse" response tables can be correlated to automatically verify the validity of glucose measurements. This technique produces additional accuracy and means of system self-calibration.

Our provisional application introduces the embodiments disclosed above, in which a black-and-white CCD array is able to collect sufficient information for blood-glucose determination — reflected electromagnetic-radiation level being distinctly correlated with glucose concentration.

This is accomplished through heavy reliance upon further electronic manipulation of the data. Such operation is mechanically and optically simpler than, and is to be distinguished from, the measurement mode that is also reported in our provisional application — and embodied in earlier prototypes of our apparatus — which employed rotating filter wheels to perform rudimentary spectral differentiation.

7. FURTHER HARDWARE DETAILS

A high-resolution black-and-white digital video camera assembly (Fig. 1) uses a charge-coupled detector (CCD) array as a sensor. The camera includes a body 10 for housing the CCD array, a mounting section 11 with an attachment thread 29, a camera bias-voltage connector 12, and a video-out connector 13.

It will be understood that all of the details presented here relate to experimental prototypes that we have built and tested. Representative dimensions for the assembly follow.

marked dimension	value (inches)	
21	2.18	
22	3.75	
23	0.75	
24	0.69	(CCD setback)
25	2.38	
26	0.75	
27	1.25	
28	1.40	

An extension tube 14 holds a 1:1.4 lens 15, making the focal length approximately 2½ cm (one inch). The purpose of the extension tube is to maximize the amount of data from

the iris 32 (Fig. 2) of the eye 30 and limit, to zero, the amount of white of the eye.

At the beginning of testing, "Snappy™" shots were selected. A Snappy, manufactured by Play Inc., is an image-capture card for a personal computer (PC). It captures a one-thirtieth-second frame from a moving image and stores it for future analysis.

Approximately forty percent of all frames were lost because of movement of the eye, reflections, and exposed white of the eye. The frames used are advantageously similar; the total digital numbers are preferably as close to each other as possible.

To produce optical data for the camera, a small electromagnetic-radiation source 33 (Fig. 2) directs electromagnetic radiation 34 toward the center of an eye 30, and reflections 35 from the pupil 31 and iris 32 traverse the lens 15 to the CCD camera 10. Note that no optical dispersing or wavelength-selecting device is included.

Thus the CCD camera 10 sees the reflected electromagnetic radiation 35 from the eye. Raw video data 37 go to a digital interface 38, which responds with corresponding digital data 39 that proceed into a computer 40.

The central-illumination arrangement of Figs. 1 and 2 was the successor to numerous earlier efforts based instead on diffuse illumination of and data collection from the eye. In the first successful, repeatable one of those (Fig. 3), electromagnetic radiation from a forty-watt incandescent party bulb 43 was integrated by flat white paint on the walls of the room itself — essentially a large integrating-sphere concept.

The electromagnetic-radiation was arranged to approach the eye 30 at a right angle to the optical axis 41 between the lens and the eye, to minimize formation of reflections and shadows. To minimize the problem of hot spots and resulting high data counts, mostly caused by bare exposed lightbulbs, the illumination was passed through a diffuser 42 — created from a plain white paper cylinder placed around the electromagnetic-radiation source.

To lessen the difficulties of repeating frames and holding the CCD camera steady, and to shield and eliminate reflections, an optical bench with a foam ocular 45 (Fig. 4) was built. In addition, a headrest (Fig. 5) helps stabilize the eye.

The optical bench, three feet long, was fashioned from two aluminum rails 47 (Fig. 4) — a rectangular one, lying horizontal, and a square bar turned on the diagonal so that one corner fits into corresponding notched grooves in the base 48 of the headrest and in the base of the camera support. The bar allows movement only along the z-axis (i. e., longitudinally). This geometry also allows setting of distances between the headrest (i. e., the eye position) and the camera.

The support stand allows up-and-down (y-axis) adjustment by means of a vertical rod with an adjustment knob. The two rails are kept parallel by being mounted on two eight-inch crossbars with three legs made from machinist jackscrews. One leg is attached to the center of the crossbar; the other two legs are attached at opposite ends of the other crossbar, thereby allowing leveling in a classical manner.

The headrest is mounted to a sliding aluminum base 48, to support two one-foot-long threaded vertical rods 54 holding a curved aluminum forehead piece 46. The whole mechanism is mounted on a centered vertical support rod 53. A crossbar 52 supports a subject's chin on a soft pad (not shown), and the forehead rests against the forehead piece 46 to stabilize the head. Adjustment and locking are facilitated by an adjustment screw 52.

The CCD camera is also mounted on a support rod, set in a commercial support stand. The rod is attached to the camera, which is inside a tubular cardboard electromagnetic-radiation shield 49 (made from a cardboard mailing tube). A trapdoor allows for adjustments to the camera with two camera-support screws through the tubular shield, centering the camera in the shield.

The tube is four inches in diameter and fourteen inches long. The trapdoor is eight inches long and sections out half of the tube, starting one inch back from the front. The camera lens face is flush with the end of the tube. The interior of the tube is painted flat white.

Various other experimental setups included some geometries with two tubes — one for each eye, with an eye-tracker disc placed in front of the eye not being sampled. We have settled, however, on a system with no ocular lens and in which the nondata eye is exposed for reasons that will become apparent.

In one experimental setup, a pair of slip-tube swing arms 69 (Fig. 6) fixed to the camera mounts — above and below the tubular shield 49 — held a vertical rod 61 on which a block 62 slides up and down 64, carrying a electromagnetic-radiation-emitting diode (LED) 63. The LED served as the electromagnetic-radiation source for central illumination. The slip tubes enabled horizontal adjustments 66, and the LED block vertical movement 64.

The next development in our experimental progression eliminated use of a mechanical eye-tracker. A video monitor is used to show real-time video of the eye being viewed for data collection.

The subject views his or her own eye on the monitor, and can rapidly correct for positioning of the eye, thus minimizing the amount of white of the eye showing — and allowing for detection of unwanted reflections. Looking at a real-time video is faster and easier than doing eye-tracking using the mechanical tracking system.

Selected single frames were stored using a frame grabber or Snappy™ image-capture card. In this process, data collection took a long time because frames with high data error — usually half of the frames taken — had to be discarded.

Next a video recorder was employed. For experimental purposes the start time, lamp color, filters, blood sugar values, commentary and end time were annotated audibly.

Four to five minutes of video data were taken continuously. The end result was thousands of frames (at a frame rate of thirty per second) from which to handpick later.

Good frames could be selected, saving a great amount of time. This also proved that the accuracy and repeatability were very high, much better than current blood-glucose meters on the market at twenty- to thirty-percent error.

Experimental work also explored numerous illumination arrangements with multiple electromagnetic-radiation sources, including arrayed LEDs of different colors in various geometries. Currently favored illumination geometry, however, as noted earlier provides a single electromagnetic-radiation source such as an LED 33 (Fig. 8).

In the best of these configurations, the LED was held centered by a diametral vane or web 72 (Figs. 7 and 8) with a hollow central hub 73 for the LED, in an aluminum bezel 71. The LED is held in front of the camera lens and aimed at the eye.

The back of the LED is covered with black tape 81 to shield the lens (surface) 15 so that none of the direct LED electromagnetic radiation is picked up by the camera. Only the electromagnetic radiation reflected by the pupil 31 and iris 32 is seen by the camera. This scheme also enables the subject to center the subject's own eye by looking directly into the LED — or a grain-of-wheat size incandescent bulb.

Bezels were made to accommodate two sizes of LED: a so-called "T1" 3mm and a "T-1¾" (5 mm). The larger LED masks the entire pupil — thereby negating the data that would be gathered for pupil calibration. The data collected is nevertheless very useful in obtaining the correction factor to establish total system linearity.

The bezel portion that goes over the lens shade has a 1.39 inch inside diameter, with a 0.05 inch wall, 0.3 inch deep. The web that holds the LED has a thickness of 0.04 inch (to minimize the masking of data from the iris to the CCD camera) and is 0.125 inch deep.

A goal during data-taking is to illuminate the iris to the point, at least, 1/2 full well on the total digital number (D/N) possible — or alternatively full well of the CCD camera. Empirical data-collection and -manipulation suggests that 1/4 full well may be a minimum needed to provide the amount of data necessary for all manipulation of calibration, subtraction and averaging for our experimental prototype system.

Whereas our experimental efforts have employed a PC for data manipulation to get a glucose value, our invention contemplates — as a first step toward portability — making a hybrid integrated circuit to replace the PC. It also appears worthwhile to develop a "foolproof" transmitter coded to transmit blood-sugar values directly to a diabetic's insulin pump, as well as calculation of utilization time and amount of insulin. Eventually continuous readings through a convenient means — such as for example eyeglass-mounted sensors — would bring the diabetic and others back to a more-normal life.

8. IMAGE-PROCESSING SOFTWARE

Two programs, "Glucon™" and "Average", were written for implementation of the present invention and were instrumental in performing research and obtaining quantitative results from our experimentation. Both programs were developed from scratch using a graphical programming language known as "G™", and also known as LabView™ 5.0 — with the IMAQ™ imaging tools.

A so-called "graphical programming language" accepts program commands, including flow of logic, not as verbal syntax but rather in the form of geometrical connections and relationships among diagrammatic elements as in Figs. 11 through 19. Such graphical entries, however, are interpreted by a compiler analogously to the way in which verbal

syntax is interpreted in use of more-traditional programming languages.

Glucon has several experimental features (filters, pixel comparison algorithms, adjustable display mode, etc.). It evolved during early experimentation phases to permit trial-and-error analysis of the image data. In the state described here, it is used to process eye image input and automatically yield the final glucose measurement as described above.

While our system is imaging a subject eye, them computer screen displays an operator control panel (Fig. 9) that includes various buttons and other controls — and also both the image presentation (at left) and the GLU or IDN values in milligrams per deciliter (mg/dL) as calculated from the images. In addition, histograms show (Fig. 10) the results of different processing stages within the program.

The G program produces the results described above. The first program, Glucon (listed in Figs. 11 through 19), is the software key to extracting information in accordance with this invention. It embodies all necessary algorithms and techniques for primary operation of the invention to obtain IDN or GLU values.

The second program, Average, is used to correlate the IDN or GLU values obtained from an imaged eye with the actual amount of patient blood sugar. It processes a user-selectable number of images of a subject eye, all taken at a particular sugar level — i. e. in quick succession.

In operation, Average creates a statistical box and then obtains the average and absolute IDN or GLU limits. These values are used to build a table of IDN-to-blood-sugar conversions.

Fig. 20 shows the on-screen operator control panel of Average. Figs. 21 and 22 represent three pages of G code that represent the entire program, Average, used to obtain calibrated IDN-to-glucose data from the IDN or GLU values.

9. GLAUCOMA MEASUREMENTS

Our work has also suggested that curvature of the iris reveals glaucoma pressure at close focal length. An eye machine can be used to automatically give difference in comparative focal lengths of inner iris vs. outer iris as an indicator of pressure.

Here the distance $F_{iris\ ID}$ (Fig. 23) represents the distance from the vertex plane of a CCD camera lens 15 to the inside diameter (ID) of the iris — in other words, to the circular transition between the iris 32 and the pupil 31. Analogously $F_{iris\ OD}$ represents the distance from the lens vertex plane to the outside diameter (OD) of the iris — i. e., to the circular transition between the iris 32 and the white 30' of the eye 30.

In the upper "A" view, these two distances $F_{iris\ ID}$ and $F_{iris\ OD}$ are substantially equal, $F_{iris\ ID} = F_{iris\ OD}$. This indicates a balanced or normal pressure condition within the eye. In the lower "B" view, the two distances are no longer equal: specifically, the ID distance now exceeds the OD distance, $F_{iris\ ID} > F_{iris\ OD}$, thereby indicating abnormal, excessive pressure.

The incremental distance 91, which is to say the difference $F_{iris\ ID} - F_{iris\ OD}$ (or ratio) between the two distances, is related to pressure. Focal determinations thus yield a measure of intraocular pressure, a large distance corresponding to high pressure and a small distance to low pressure. Depth of field, for example 0.3 mm (0.012 inch), may form a limitation on this technique.

It will be understood that the foregoing disclosure, and that of the following Appendix, are intended to be merely exemplary, and not to limit the scope of the invention — which is to be determined by reference to the appended claims.

WHAT IS CLAIMED IS:

1. Noninvasive apparatus for measuring blood-sugar concentration in a body by measuring electromagnetic-radiation reflectivity from the body; said apparatus comprising:

means for directing electromagnetic radiation to such body; and

means for receiving and measuring electromagnetic radiation reflected from such body substantially without spectral analysis of the reflected electromagnetic radiation.

2. The apparatus of claim 1 for use in measuring electromagnetic radiation reflectivity from an eye of such body, wherein:

the directing means direct electromagnetic radiation to such eye; and

the receiving and measuring means comprise means for receiving and measuring electromagnetic radiation reflected from such eye.

3. The apparatus of claim 1, wherein the receiving and measuring means comprise:

a monochrome detector array.

4. The apparatus of claim 3, wherein:

the monochrome detector array comprises a black-and-white CCD camera.

5. The apparatus of claim 4, wherein:

the receiving and measuring means comprise a digital processor for analyzing signals from the CCD camera.

6. The apparatus of claim 1, wherein:

the receiving and measuring means comprise a digital processor for analyzing signals representative of quantities of the reflected electromagnetic radiation.

7. The apparatus of claim 6, wherein:

the digital processor is part of a personal computer; and

the blood glucose level is reported on a monitor screen of the computer.

8. The apparatus of claim 6, wherein:

the apparatus is a handheld portable unit;

the unit comprises reporting means for indicating the blood glucose level; and

the digital processor is part of the handheld portable unit.

9. The apparatus of claim 8, wherein:

the reporting means comprise an LCD unit for visually indicating the blood glucose level.

10. The apparatus of claim 1, wherein:

the receiving and measuring means comprise means for detecting change in level of the reflected electromagnetic radiation and relating said change to blood-glucose concentration.

11. The apparatus of claim 1, wherein the receiving and measuring means comprise:

means for detecting change in level of the reflected electromagnetic radiation; and

means for reporting glucose concentration as a substantially monotonic response to reflected-electromagnetic-radiation level.

12. The apparatus of claim 1, wherein the detecting means comprise:

means for responding to reflected visible electromagnetic radiation.

13. The apparatus of claim 1, wherein the detecting means comprise:

means for responding to electromagnetic radiation in the yellow or yellow-green portion of the spectrum, or both.

14. The apparatus of claim 1, wherein:

the means for receiving and measuring substantially without spectral analysis comprise means for eliminating response to electromagnetic radiation in the red or infrared, or both.

15. The apparatus of claim 1, wherein:

the means for receiving and measuring substantially without spectral analysis do take into account a reverse signal response in the red or infrared, or both.

16. Noninvasive apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from the body; said apparatus comprising:

a self-contained case;

means, mounted to the case, for directing electromagnetic radiation to such body; and

means, mounted to the case, for receiving and measuring electromagnetic radiation reflected from such body.

17. The apparatus of claim 16, wherein:

the case is fully portable.

18. The apparatus of claim 16, wherein:

the case fits in the palm of a normal-size adult's hand.

19. Noninvasive apparatus for measuring blood-sugar concentration in a body by measuring electromagnetic-radiation reflectivity from an eye of the body; said apparatus comprising:

means for directing electromagnetic radiation to an iris of such eye;

means for receiving and measuring electromagnetic radiation reflected from such iris; and

a programmed digital processor for analyzing the measured reflected radiation and computing blood-sugar concentration therefrom;

wherein the programmed processor comprises means for using a reflection of the electromagnetic-radiation source, from such eye, as a peak amplitude point for image alignment.

20. The apparatus of claim 19, wherein the receiving and measuring means also comprise means for receiving and measuring electromagnetic radiation from a pupil of such eye, for determination of:

a baseline dark level, or

an illumination level provided by the electromagnetic-radiation directing means, or

both said baseline dark level and said illumination level.

21. A blood-glucose measuring method comprising the steps of:

imaging forward surfaces of a person's eye on an electronic camera;

digitizing resultant image signals from the camera;

to determine blood-glucose level, processing pixel signals representing the iris, separately from pixel signals representing other parts of the eye.

22. The method of claim 21, further comprising the steps of:

processing pixel signals representing the pupil to obtain a baseline dark level or an illumination level, or both; and

applying the dark level or illumination level, or both, to refine the pixel signals representing the iris.

23. The method of claim 22, wherein the processing step comprises:

applying average reflected intensity level of the pupil to represent the dark level baseline.

24. The method of claim 21, wherein:

the iris-pixel signal processing comprises integrating all usable iris-pixel signals to produce a unitary intensity indication.

25. The method of claim 24, wherein:

the applying step comprises integrating into said indication only intensities that are higher than that of the pupil.

26. The method of claim 21, further comprising the step of:

substantially removing image scene and illumination variation.

27. The method of claim 21, further comprising the step of:

calibrating readings for an individual patient.

28. The method of claim 21, further comprising the step of:

masking out the pupil pixels from the iris region.

29. The method of claim 28, wherein:

the masking step comprises applying a software pupil mask that substantially stabilizes the number of iris pixels available for use and substantially stabilizes pupil centering within the iris image.

30. The method of claim 29, wherein:

the pupil mask is larger than the largest pupil diameter occurring in measurement conditions.

31. The method of claim 21, further comprising the step of:
masking out the pupil pixels from the iris region.

32. The method of claim 21, further comprising the step of:
diffusing source electromagnetic radiation to minimize hot spots.

33. The method of claim 21, further comprising the step of:
removing peak signal amplitudes, to minimize the effect of illumination hot spots.

34. The method of claim 21, further comprising the step of:
mapping illumination hot spots, to enable disregarding hot-spot regions in said processing step.

35. The method of claim 21, further comprising the step of:
adjusting image contrast to substantially fill the complete dynamic range of pixel data words.

36. The method of claim 21, further comprising the step of:
looking up the measured level in a lookup table to obtain a corresponding numerical blood-glucose concentration indication in quantity of glucose per unit blood volume.

37. The method of claim 21, wherein:
said digitizing step comprises distinguishing electromagnetic-radiation-intensity changes at least as small as one part in ten thousand.

38. The method of claim 21, comprising these steps:

finding a centroid of the pupil of the eye;

calculating average brightness around the pupil centroid;

masking out the pupil region of the eye;

equalizing the iris image using the pupil brightness as a level baseline;

removing hot spots if present;

integrating all of the processed iris pixels to obtain a numerical representation of brightness level of the iris;

searching a lookup table to apply a previously developed calibration and thereby determine an imputed glucose concentration in quantity of glucose per unit volume; and

displaying the imputed glucose concentration.

39. A blood-glucose measuring method for use with a small electromagnetic-radiation source and comprising the steps of:

automatically finding a reflection, from a patient's pupil, of the electromagnetic radiation; and

automatically performing a position alignment based upon the location of said reflection of the electromagnetic radiation.

40. The method of claim 39, further comprising the step of:

zeroing-out the area within the electromagnetic-radiation source, to form an image of forward surfaces of the eye without the electromagnetic-radiation source.

41. The method of claim 39, for use with a centrally disposed electromagnetic-radiation source and further comprising the step of:

growing a pupil mask, starting from the electromagnetic-radiation source as a centerpoint, to cover the pupil area in the image.

42. The method of claim 41, further comprising the step of:

capturing brightness level in an area under the aligned pupil mask for use in a dark-level calibration.

43. Apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from an eye of the body; said apparatus comprising:

a detector array;

a small electromagnetic-radiation source held directly in front of the detector array, for directing electromagnetic radiation to such eye; and

means for receiving and measuring electromagnetic radiation reflected from such eye.

44. The apparatus of claim 43, further comprising:

a lens between the detector array and the electromagnetic-radiation source.

45. The apparatus of claim 44, wherein:

the electromagnetic-radiation source shines toward the eye from substantially the geometric center of the lens.

46. The apparatus of claim 43, wherein:

the electromagnetic-radiation source shines toward the eye from substantially the effective geometric center of the array.

47. The apparatus of claim 46, further comprising:

means for using a reflection of the electromagnetic-radiation source, from such eye, as a peak amplitude point for finding the image center.

48. The apparatus of claim 43, for use in measuring blood glucose concentration for such body of a human being; and wherein:

the electromagnetic-radiation source is a visual centering target for the human being;

wherein, to take a measurement, the human being looks substantially directly toward the electromagnetic-radiation source.

49. Apparatus for measuring blood-sugar concentration in a living body by measuring electromagnetic-radiation reflectivity from blood of the body; said apparatus comprising:

means for directing electromagnetic radiation to such blood; and

means for receiving and measuring electromagnetic radiation reflected from such blood substantially without spectral analysis of the reflected electromagnetic radiation.

50. A noninvasive method for measuring intraocular pressure by measuring electromagnetic-radiation focal characteristics for forward surfaces of the eye; said method comprising the steps of:

finding focal distances to the inner and outer diameters of the iris respectively; and

interpreting discrepancy between said focal distances as a measure of said pressure.

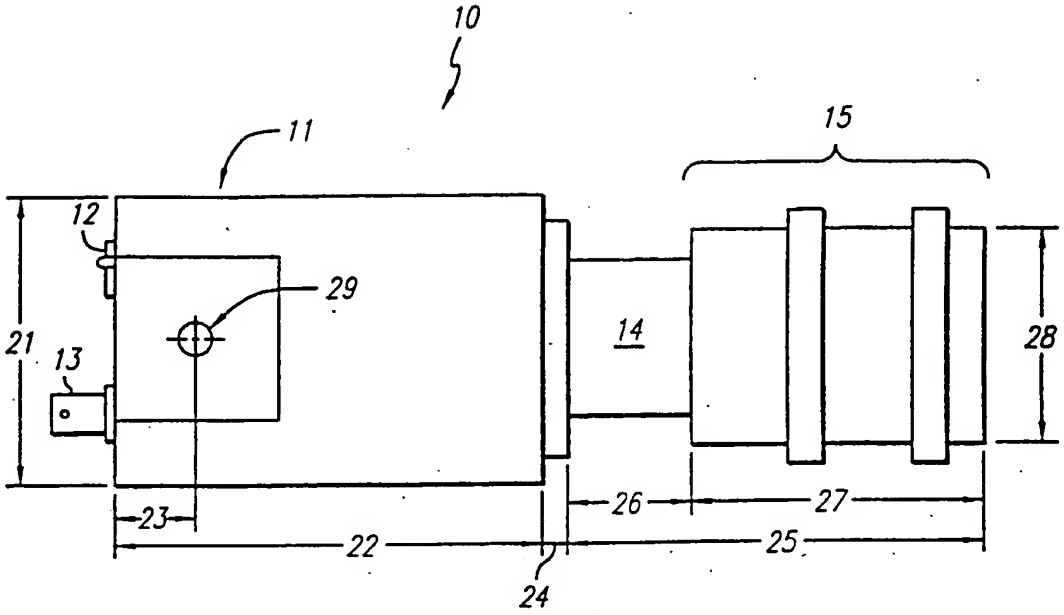

10
11
15
12
29
21
13
14
28
23
26
27
22
25
24

FIG. 1

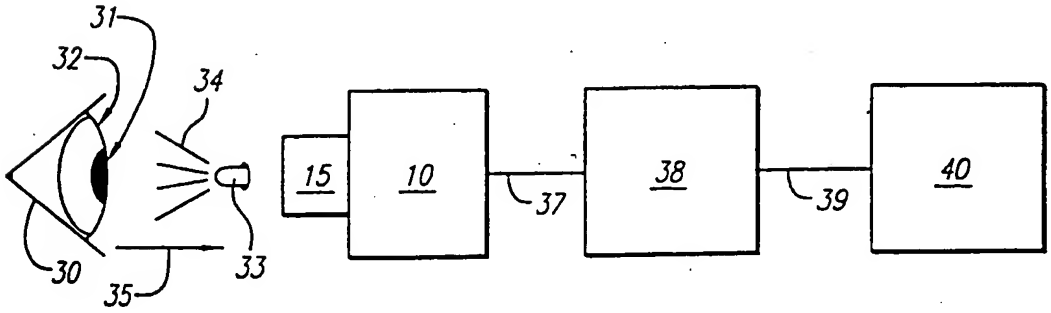

31
32
34
15
10
38
40
37
39
30
35
33

FIG. 2

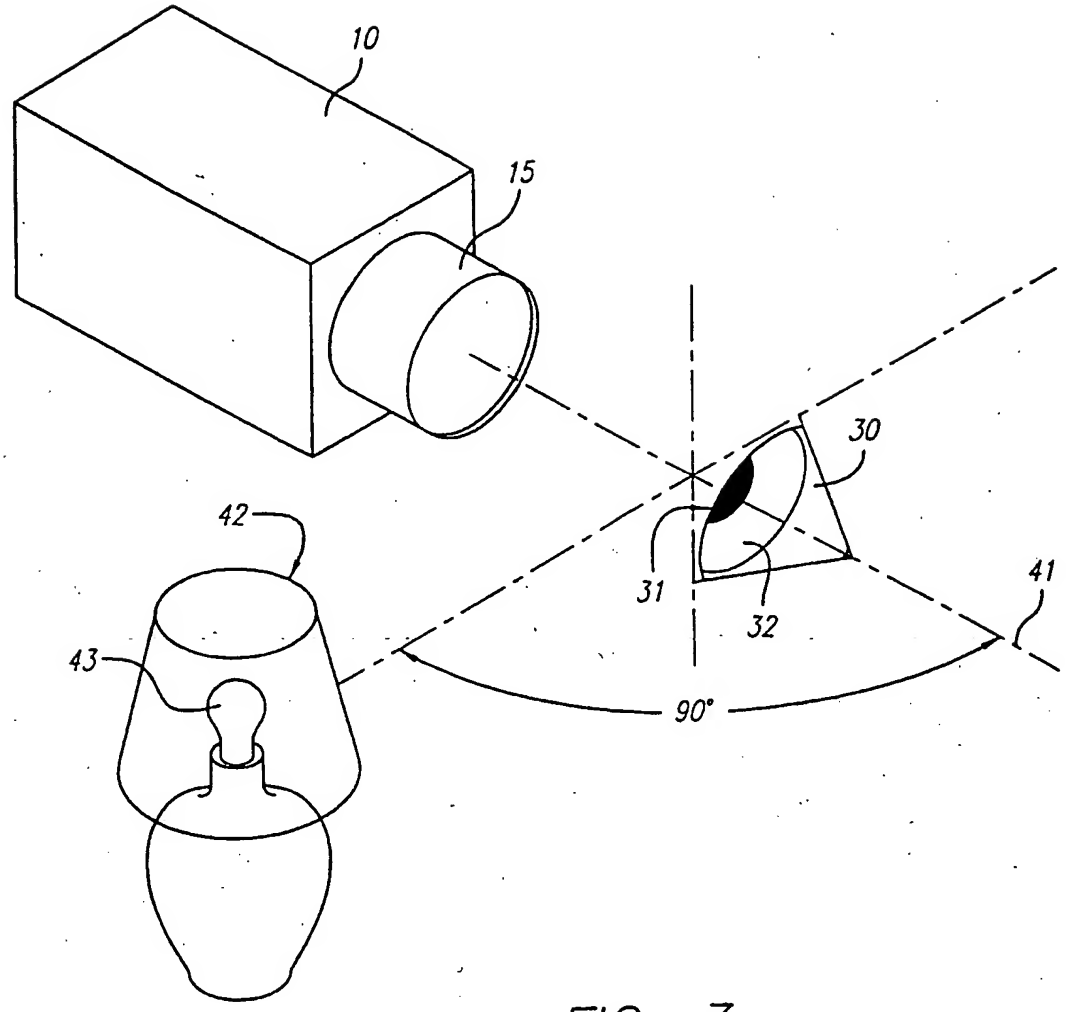


FIG. 3

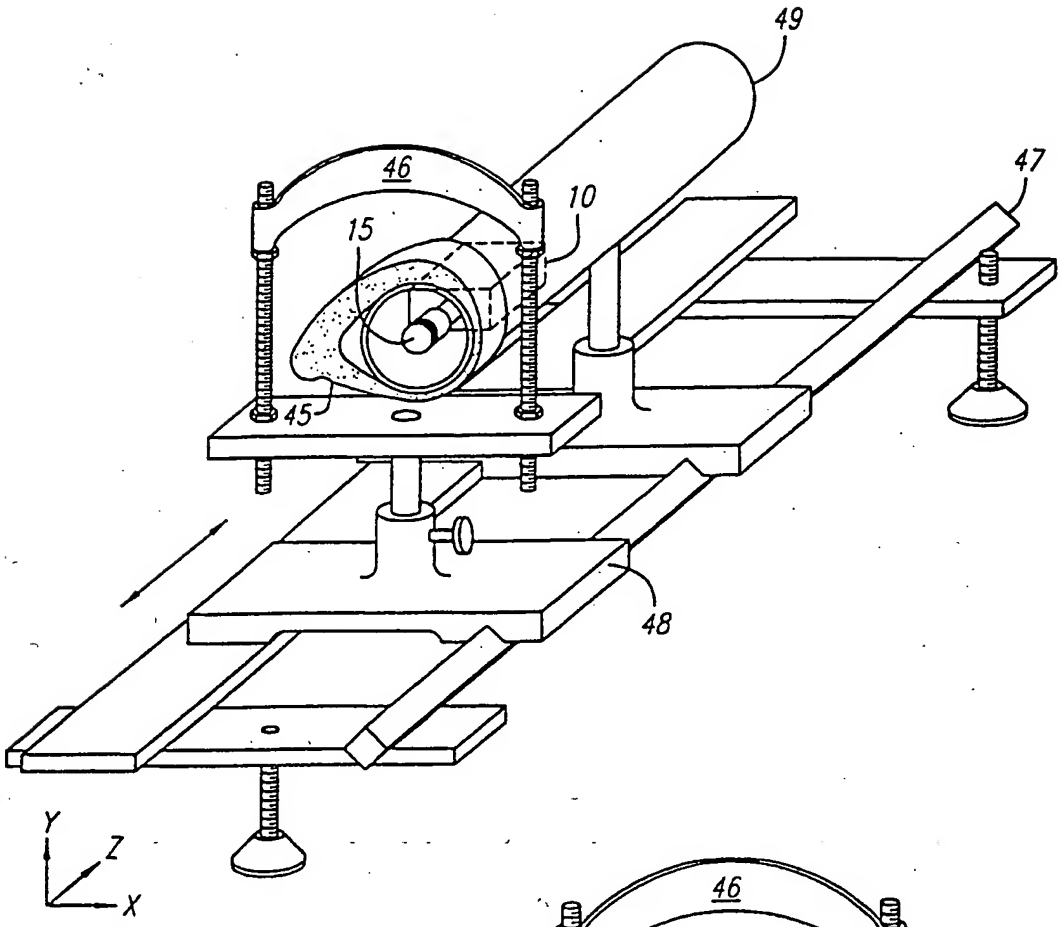


FIG. 4

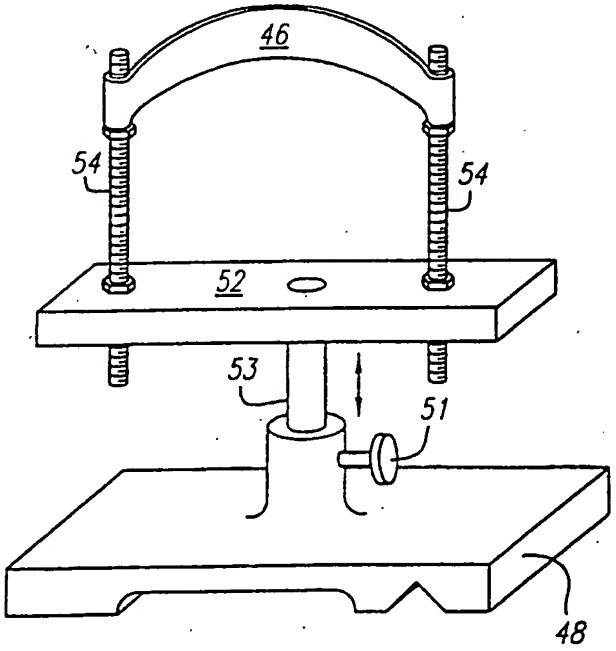


FIG. 5

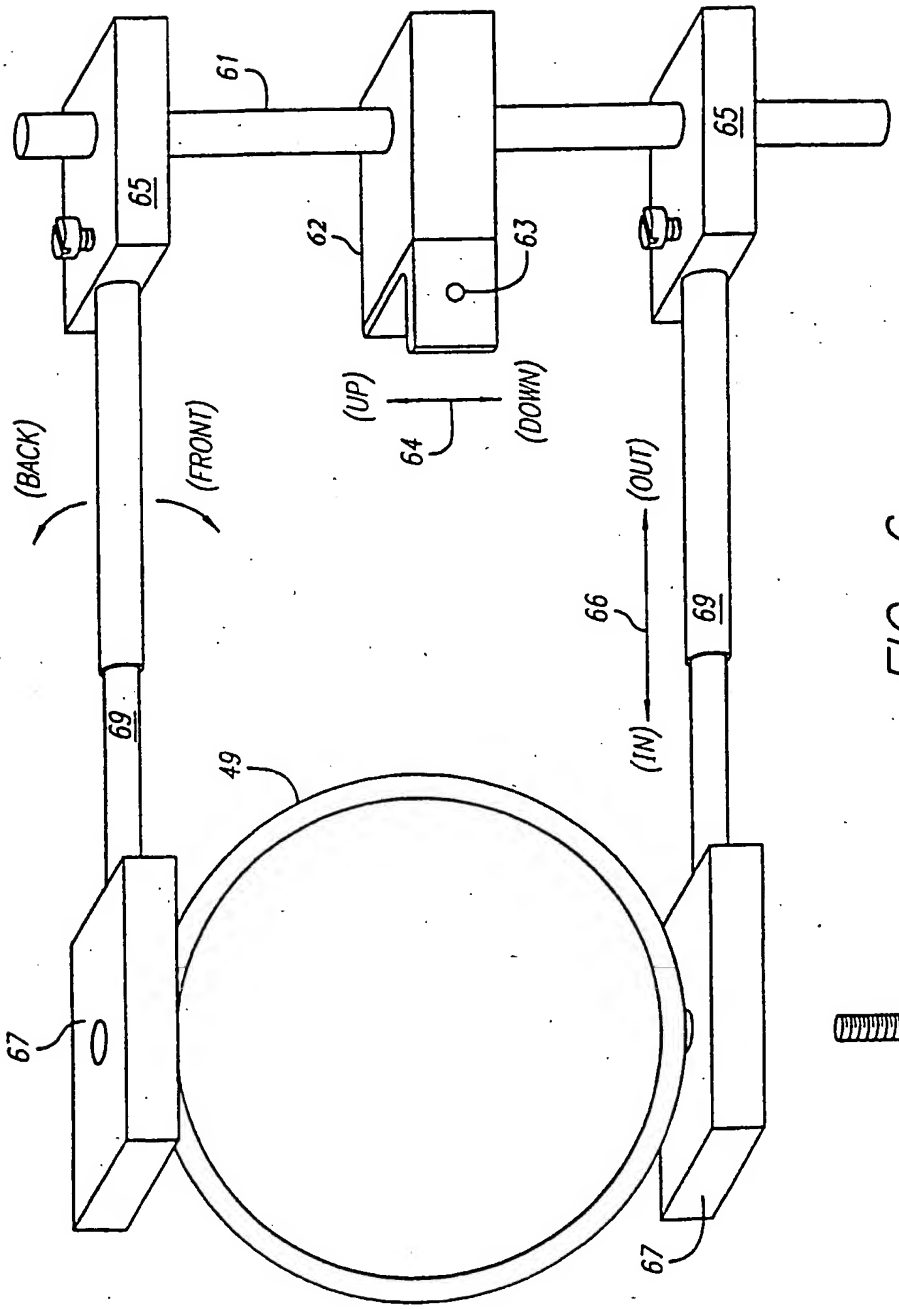


FIG. 6

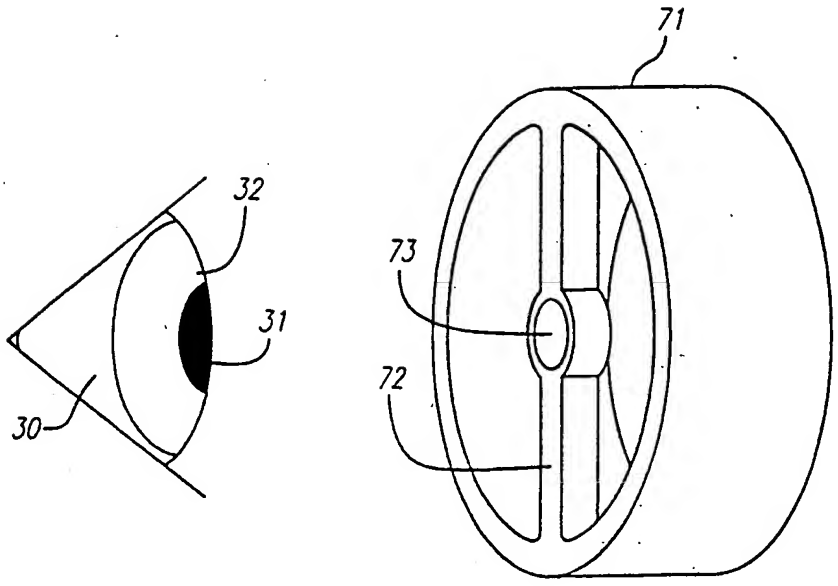


FIG. 7

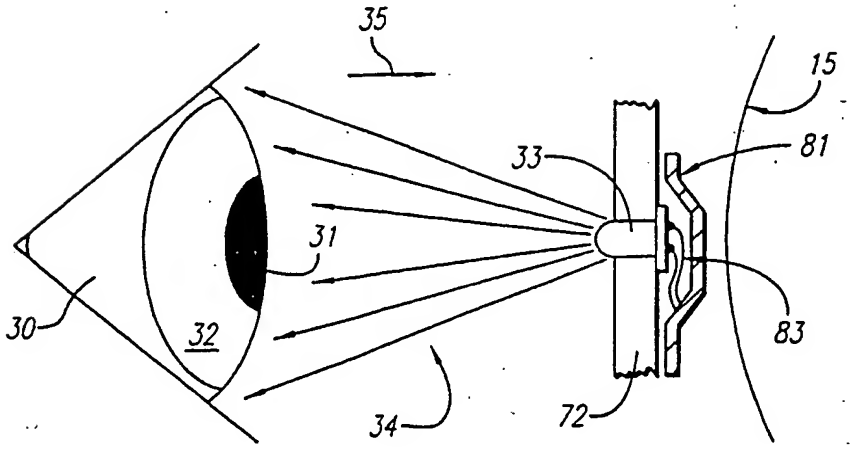


FIG. 8

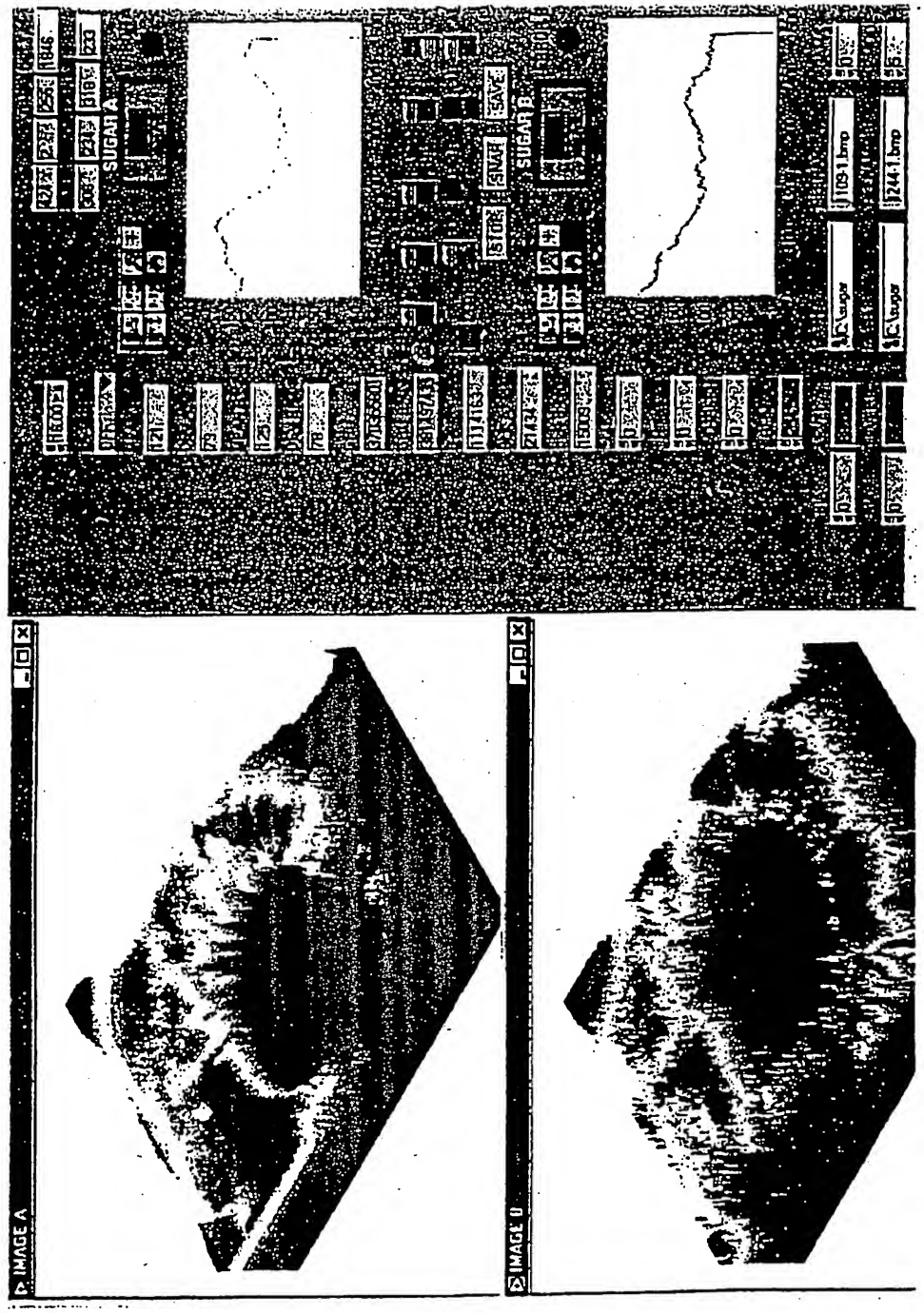


FIG. 9

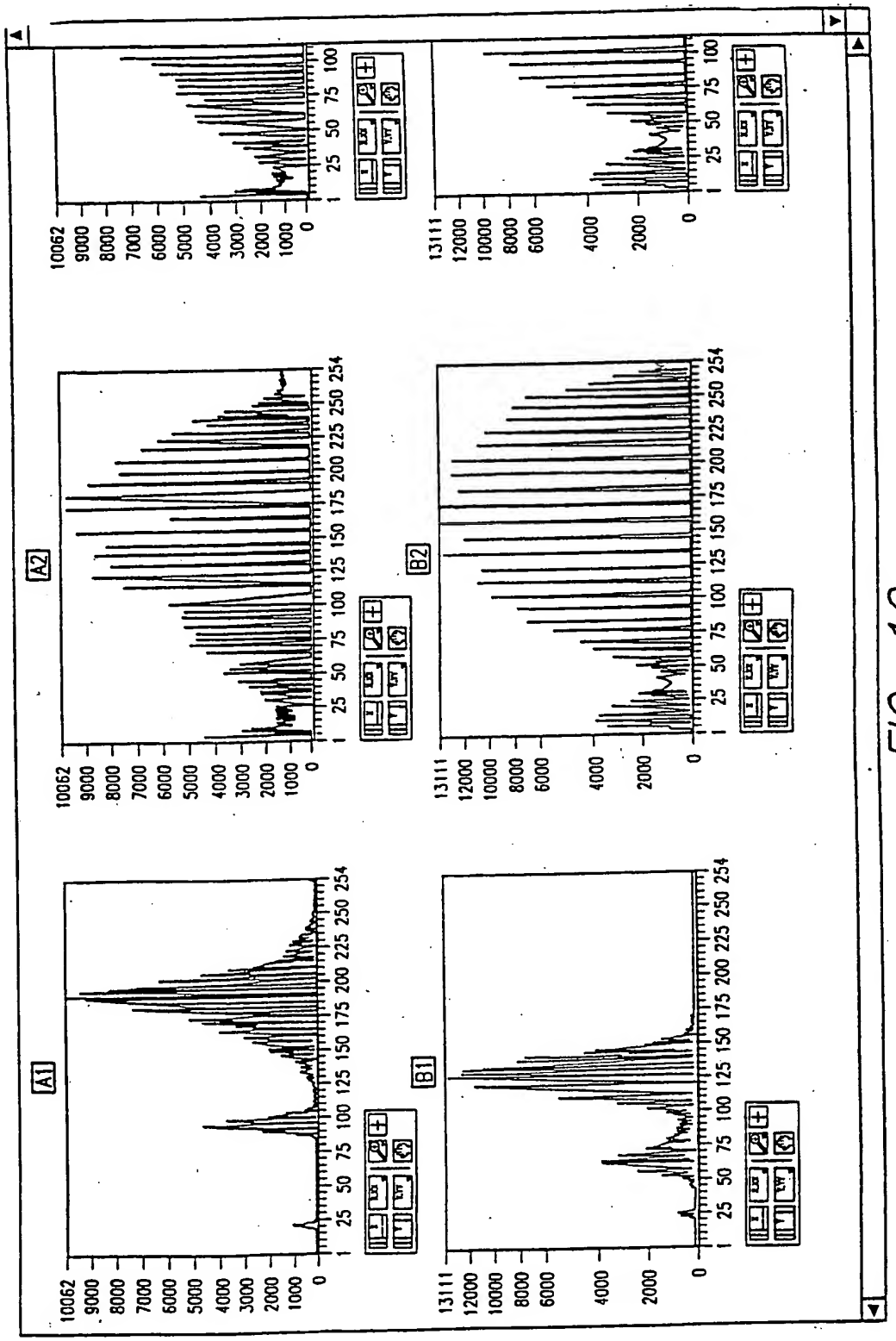


FIG. 10

FIG. 11

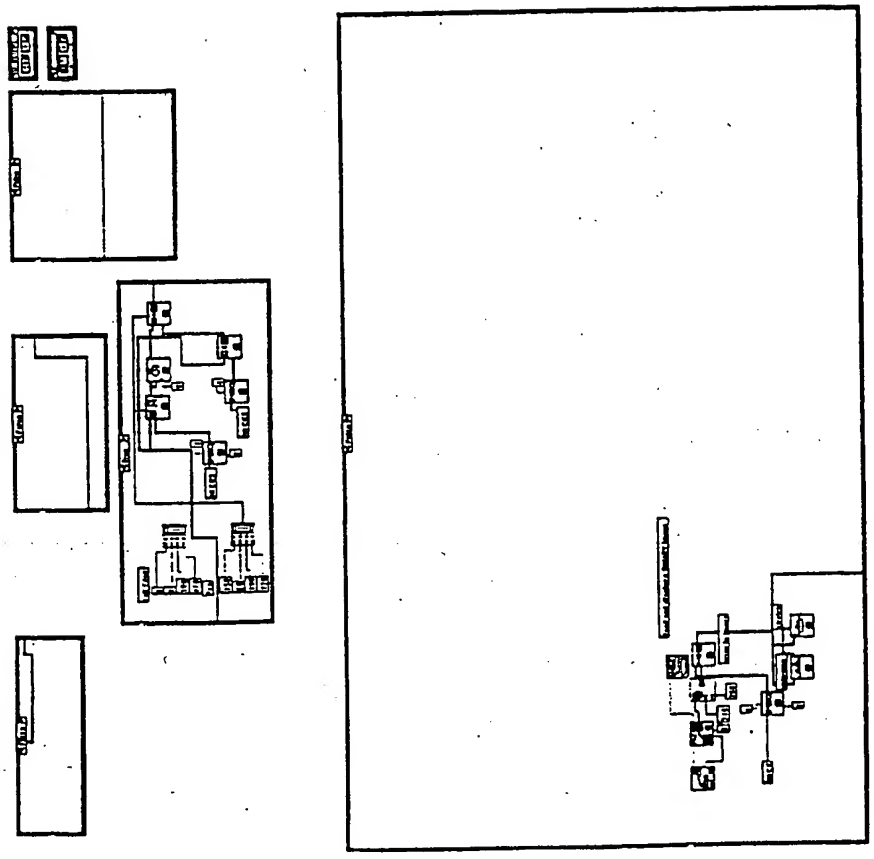


FIG. 12

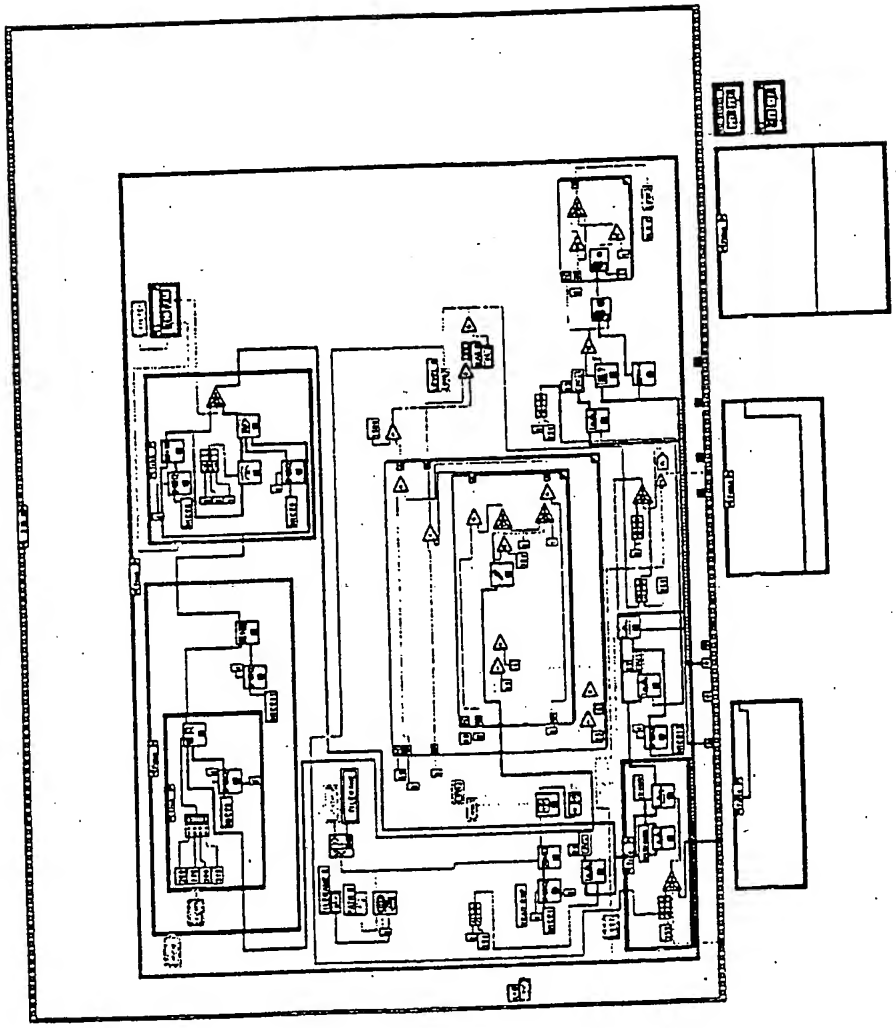


FIG. 13

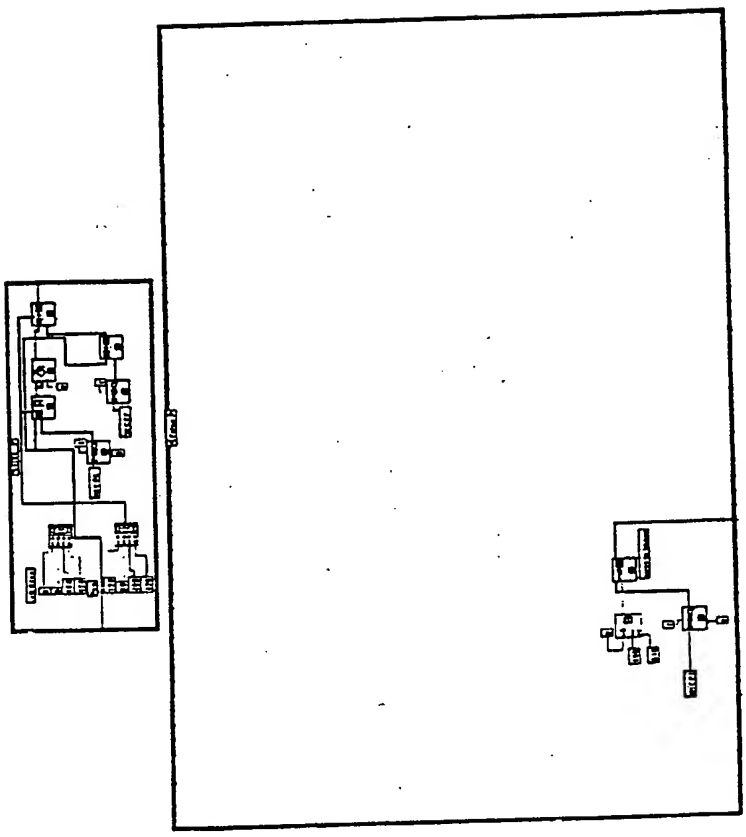


FIG. 14

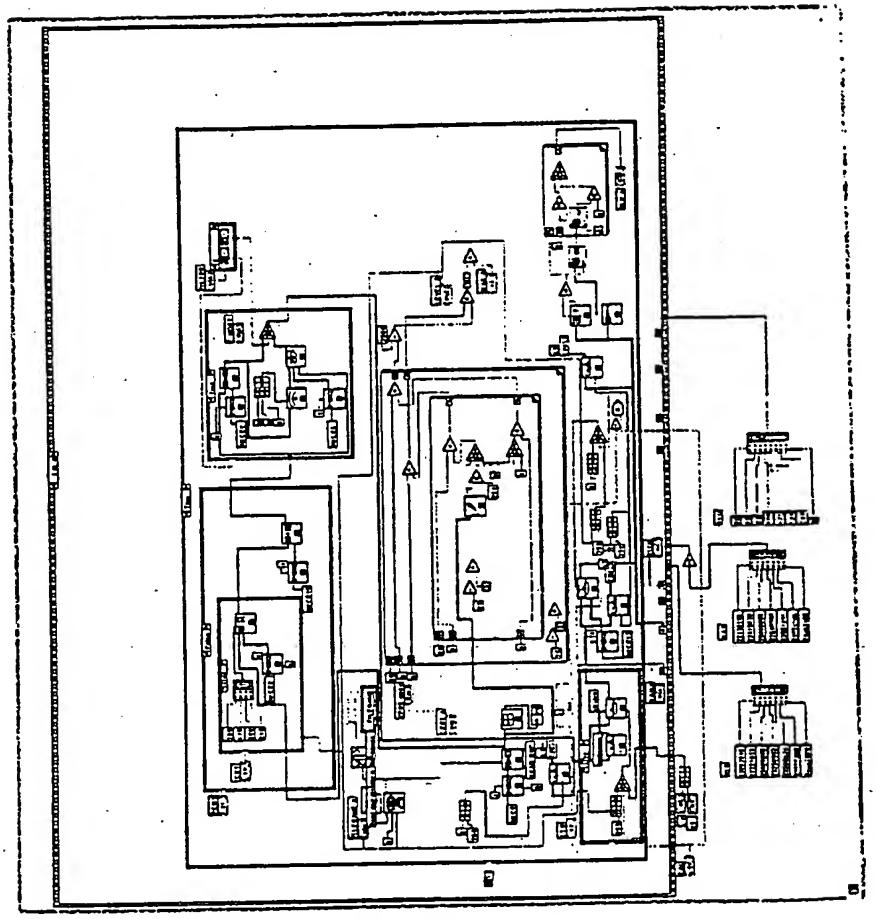


FIG. 15

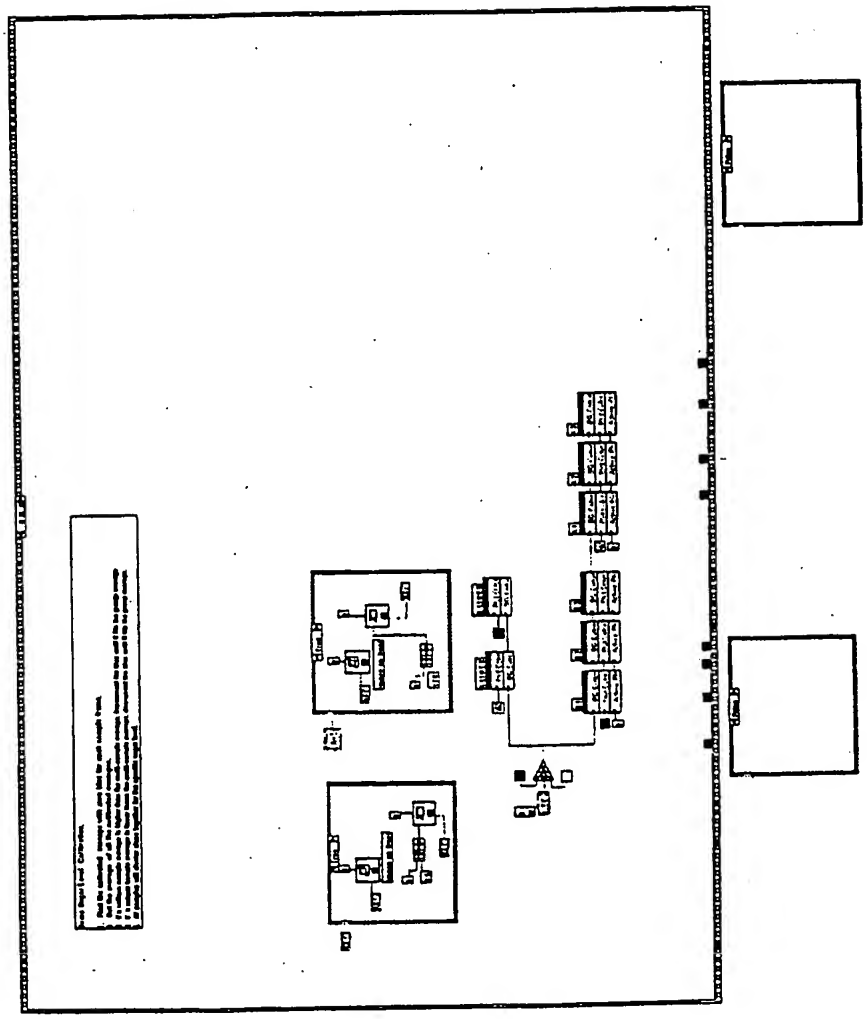


FIG. 16

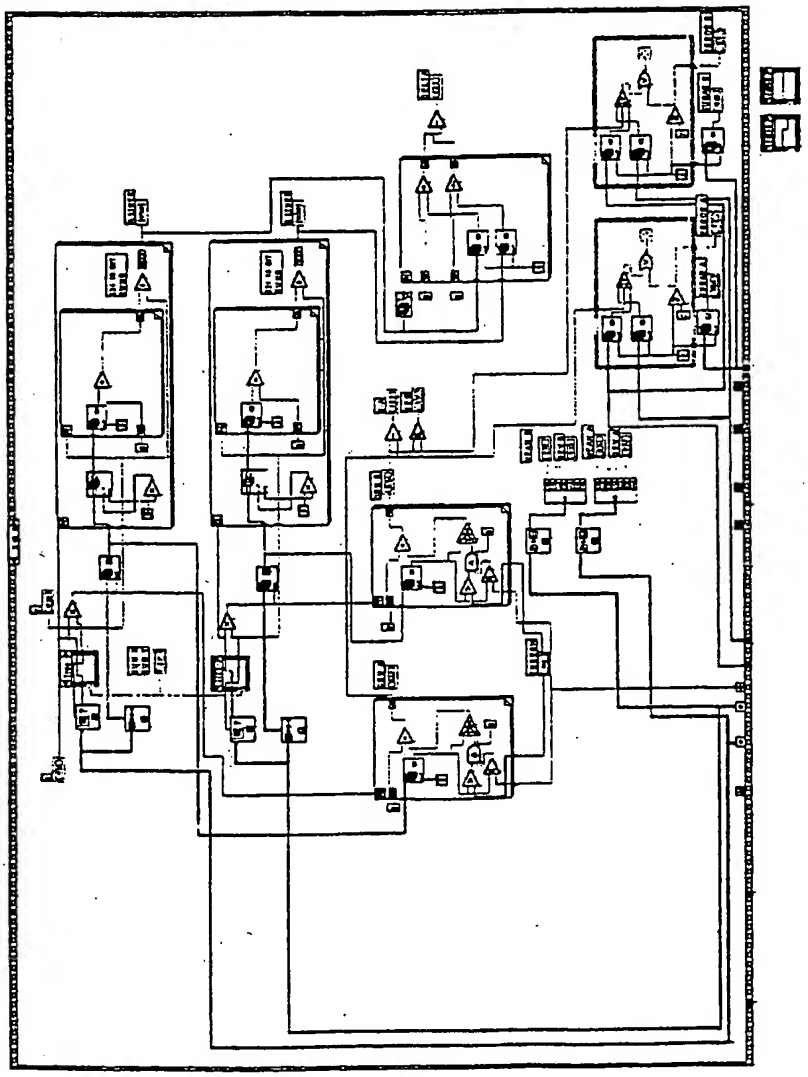


FIG. 17

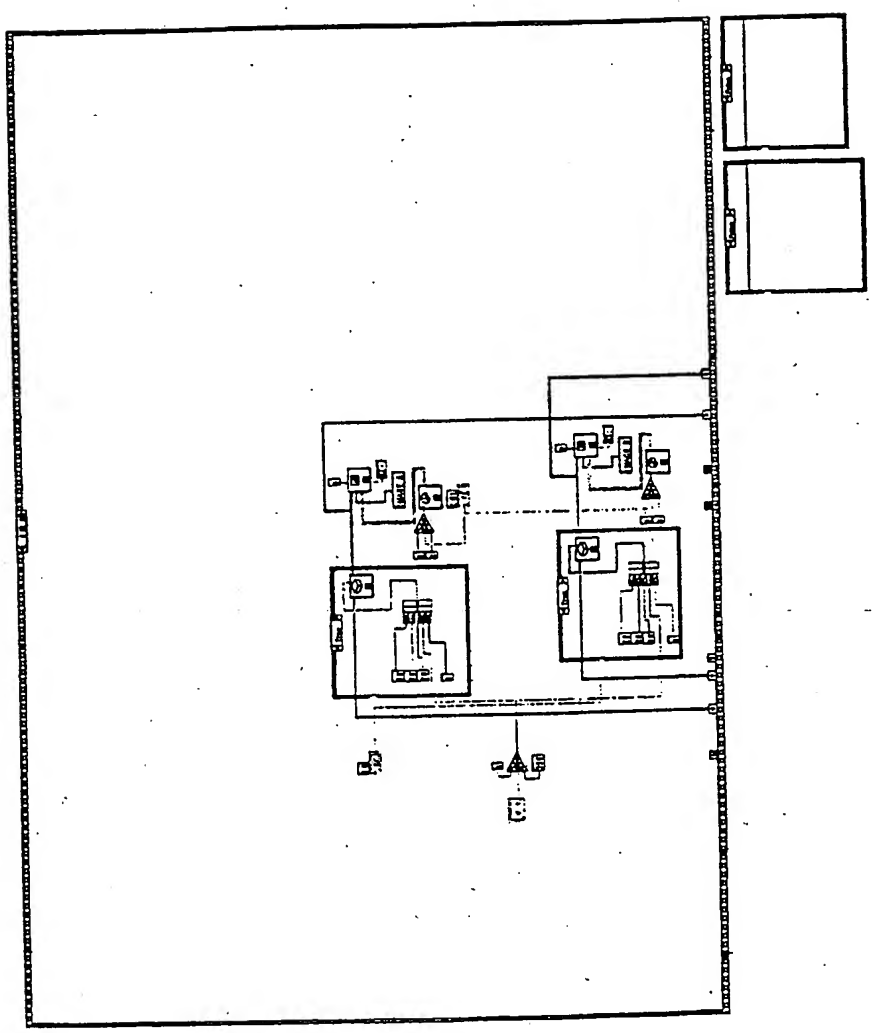


FIG. 18

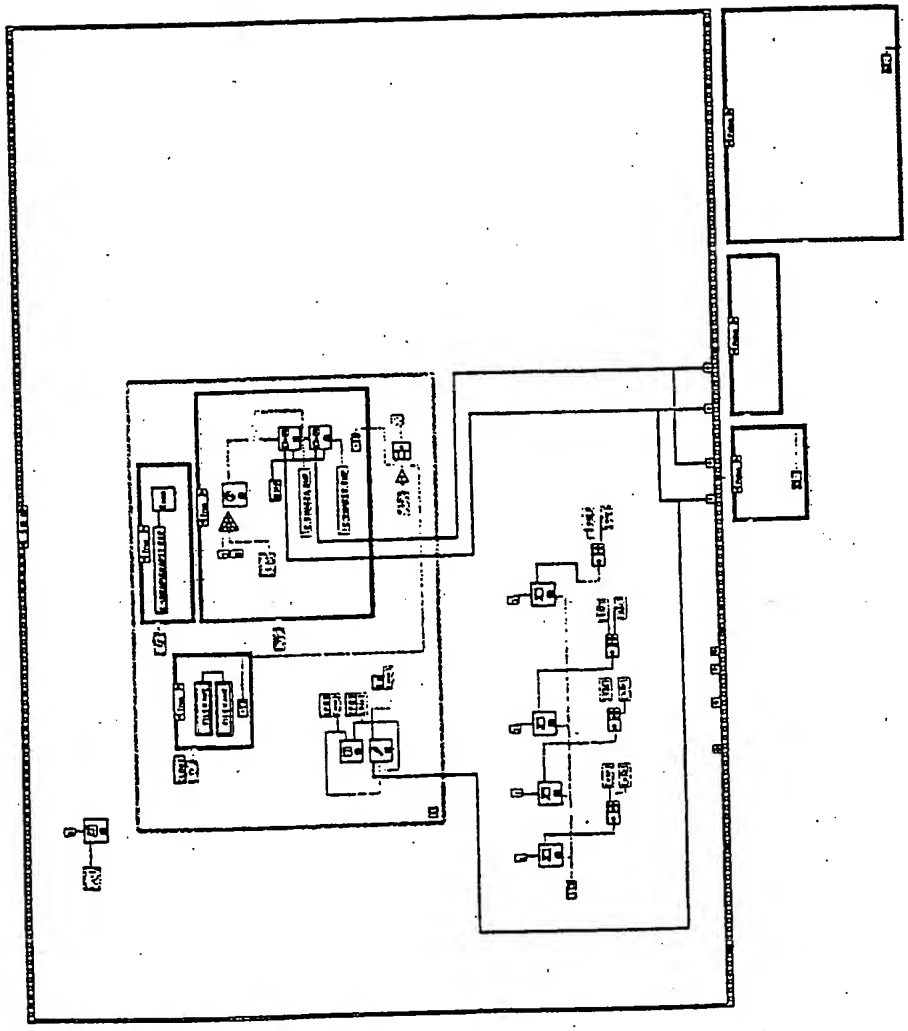
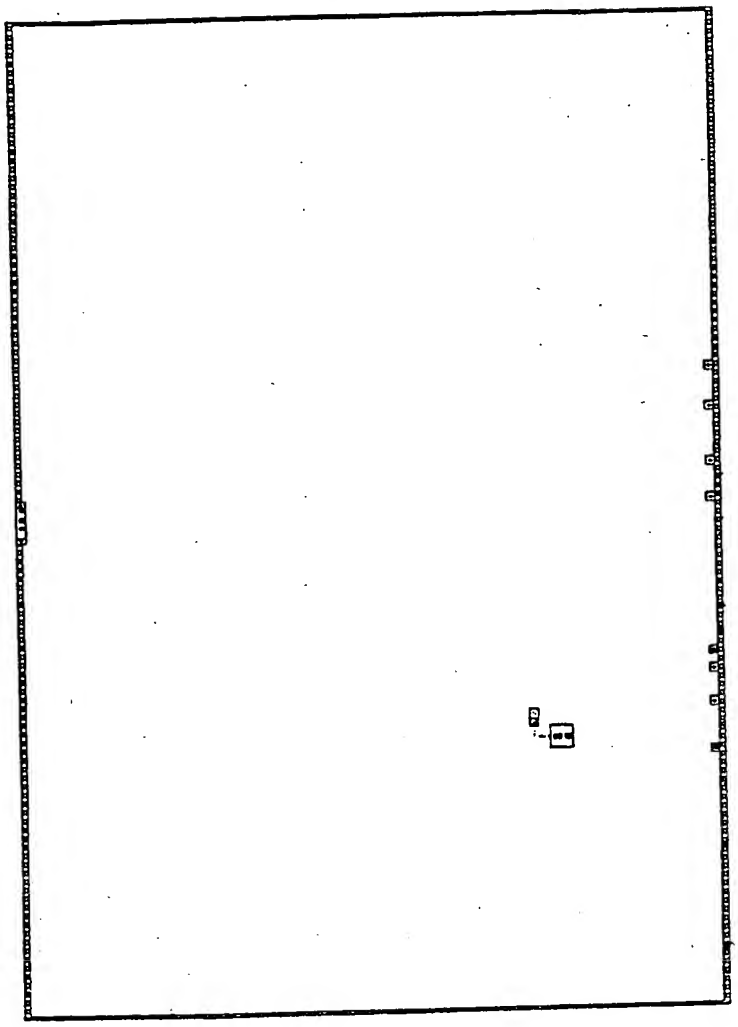


FIG. 19



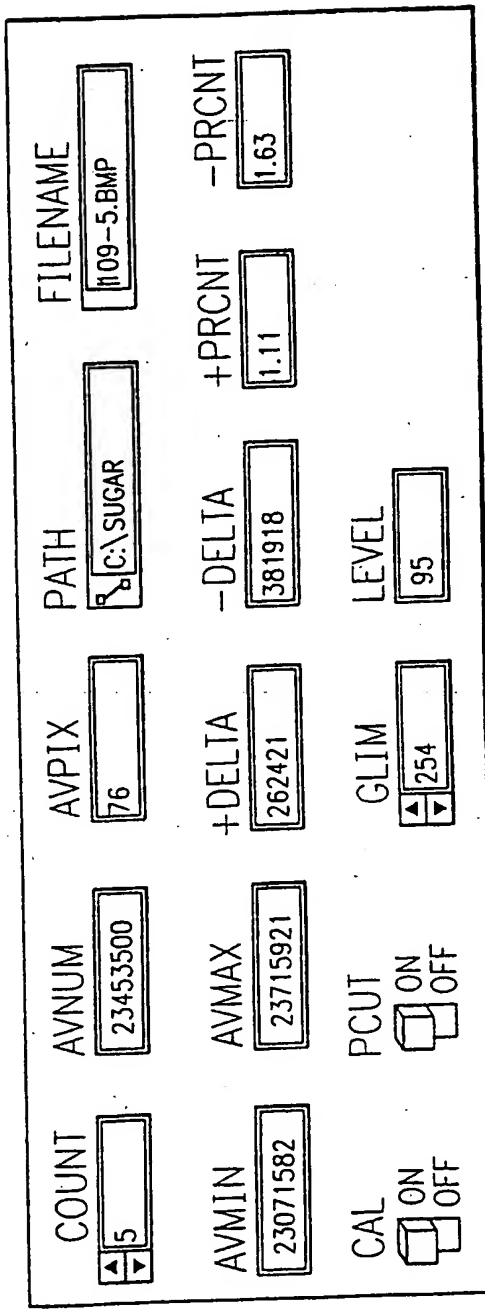
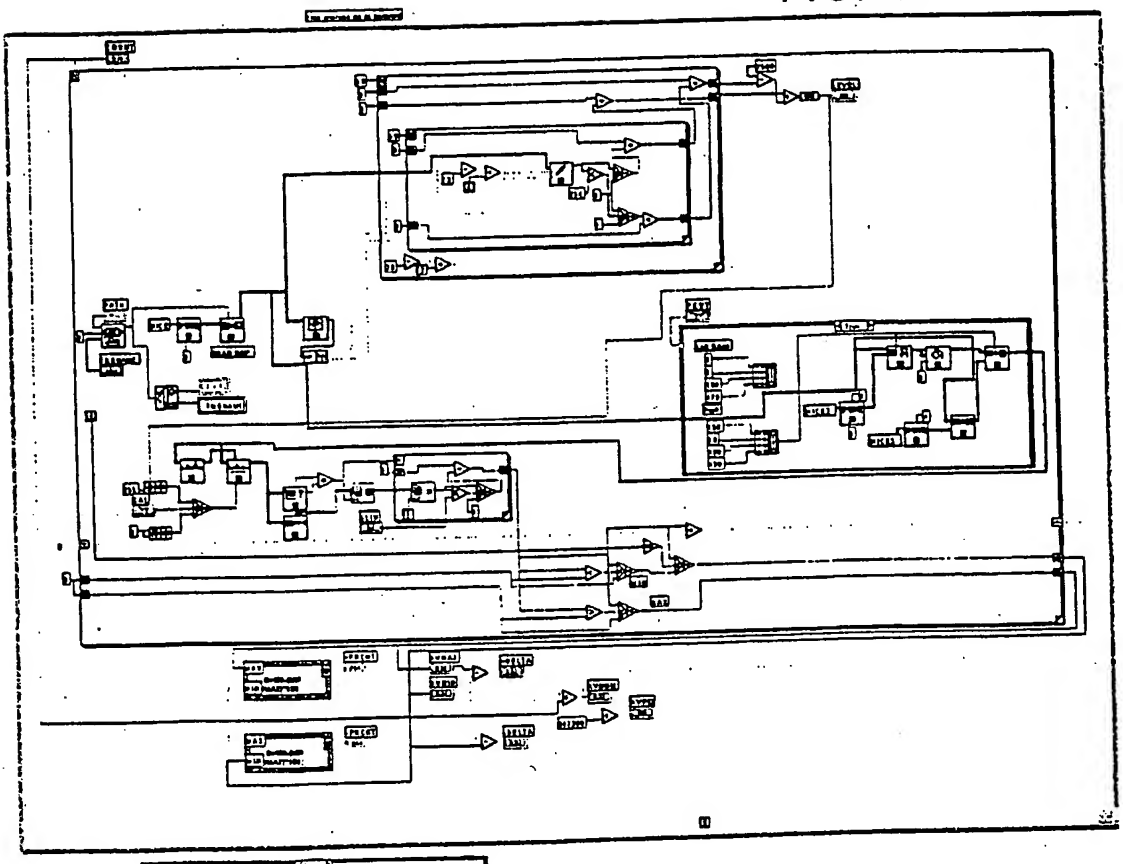

COUNT
5
AVNUM
23453500
AVPIX
76
PATH
C:\SUGAR
FILENAME
109-5.BMP
AVMIN
23071582
AVMAX
23715921
+DELTA
262421
-DELTA
381918
+PRCNT
1.11
-PRCNT
1.63
CAL
ON
OFF
PCUT
ON
OFF
GLIM
254
LEVEL
95

FIG. 20

FIG. 21



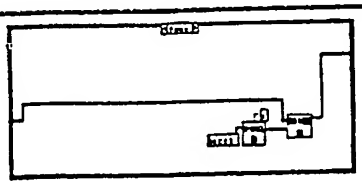
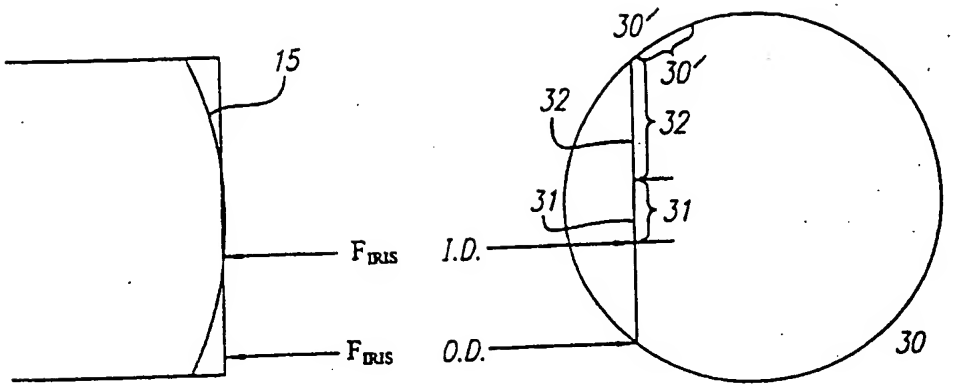
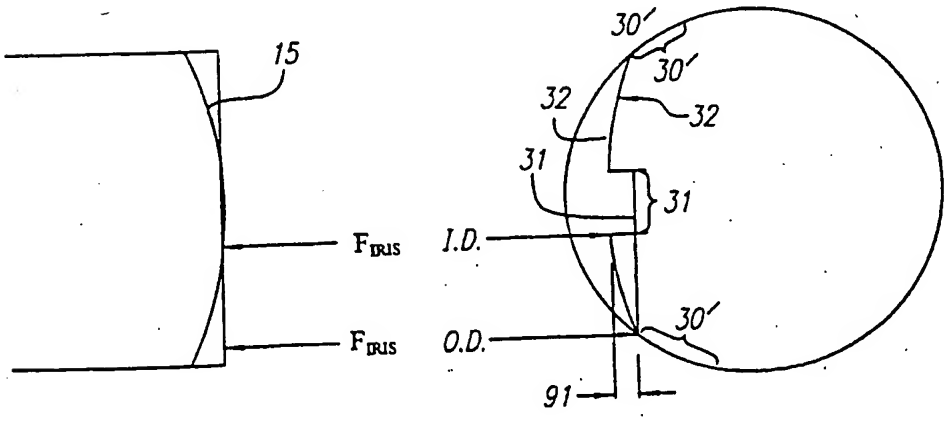


FIG. 22



NORMAL PRESSURE

FIG. 23A



EXCESSIVE PRESSURE

FIG. 23B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21680

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/05
US CL :600/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/310, 316, 345, 347, 456, 365

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,569,186 A (LORD et al.) 29 October 1996, entire document.	1-50
A	US 5,329,931 A (CLAUSON et al.) 19 July 1994, entire document.	1-50

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
12 JANUARY 2000

Date of mailing of the international search report
10 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
RYAN CARTER

Telephone No. (703) 308-2990